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EDITORIAL

THE PAST AND THE FUTURE

DENTISTRY can look back on exceptionally significant developments during the century that the American Dental Association has been in existence. The techniques of the dental art have kept in step with the advent of modern materials. Science, the basis for the understanding of disease as well as for the development of new therapeutic methods, has disclosed facts previously hidden. Pathology, the queen of the sciences, came into full bloom during this period. The microscopic study of oral diseases and the use of the electron microscope for the investigation of dental tissue have been significant. Research discoveries and their application have so increased our sphere of activity that the horizon of dentistry has enlarged in all directions. No longer can the general practitioner give satisfactory service in all the new areas which have sprung up. The necessity for graduate training for those who desire to enter a specialty practice has arisen. At the end of the first century of organized dentistry, therefore, we have a division of responsibility, with the patient protected by requirements concerning training of specialists and the establishment of board examinations to accredit those capable and expert in the various branches of dentistry.

Will this excellent past be followed by an equally brilliant future? What will dentistry be like in 2059?

The tendency of dentists to establish suburban practices has been noticed during the last few years, and I can see that the drift of dental practice from city centers to the suburbs will be accelerated. Probably groups of specialists will practice together in a large, well-designed building—a so-called "stomatarium"—which will be equipped with landing platforms for "taxicopters" and larger "dentocopters" by means of which those who work or dwell in the neighboring city will be brought punctually to the clinics. By means of a "descentorator," the patients will be brought down to the various floors where different types of odontotherapy will be performed. Many, however, will mount in elevators to "solio" rooms in a high tower above the mist and smog for

prophylaxis and therapy involving the newest methods, including odontic irrigations with mineralized water and exposure to new cosmic rays used for their antiodontolytic action, especially in the treatment of periodontal diseases and other mouth infections.

Periodontics will have expanded and will have taken on much greater importance than it has to date. Because of the ever-increasing deleterious effect of atomic fall-out on the odontogenic epithelium, anodontia will have become a new and distressing plight. The implantation of teeth will have become one of the important research problems of the time. After the expenditure of enormous sums for investigative work, the artificial culture of tooth germs may have become perfected toward the end of the century. Cultodontic laboratories will have been established to grow, in vitro, embryonic tooth germs from odontogenic epithelium and mesenchymal cells injected into a hemato medium prepared with admixtures from the recipient's blood. By careful selection of the donor tissue, it will have become possible to culture teeth of various anatomic shapes and sizes, the eruption of these teeth to be supervised by a skillful orthodontist who will guide them into the right position in the dental arch.

The oral surgeon will have developed new methods for lengthening the mandible, because the lack of growth stimulation by odontogenesis will have produced retrognathic individuals instead of the prognathic ones seen today. The underdeveloped jaw will have contributed to psychologic distress in those affected, and a great demand will have arisen for surgical correction.

Endodontics will have become an obsolete science, both because of the excellent progress made in the prevention of caries by the prophylactic therapy mentioned and because of the natural obliteration of the dental pulp by the ingested strontium, an important part of the atomic fall-out which will have contaminated food consumed by domesticated animals and by man. The calcification of the pulp tissue will also have decreased remarkably the amount of odontogenic infection, since the pathway from an open cavity to the periapical tissue will have become nonexistent in most persons after the second decade of life.

The periodontist involved in the treatment of a disease of great progressiveness which shows a tendency to resist all efforts at therapy will, in spite of the new physiotherapeutic treatment, encounter an additional handicap in that the crevicular epithelium will have become affected by the water contaminated in many regions with atomic substances. The combination of excellent periodontal therapy with denture splints will have been found inadequate, and the partial or total loss of the teeth will have greatly stimulated new developments in methods of implant dentures. Here, as in other fields, the corporation of various specialists will have again become a necessity. The exodontist will now have become an implantationist, but the prosthodontist will have to have cooperated in order to furnish the specially constructed dentures which frequently will have to be redesigned.

Education will have assumed much broader scope. Stomatology rather than dentistry will be featured. Many new diseases will have become common.

Antibiotics will have lost their effect; only sturdy antibiotic-resistant fungi and microorganisms will have survived, and only the new rays from each end of the light spectrum will be affecting them.

The problem of maintaining top-flight teaching staffs with which the universities have been confronted for some time will have been partly solved. In the past it has been difficult to induce graduates to embark on a teaching career. This was due principally to the poor comparison of the economic status of university professors with that of the practicing dentist and dental specialist and the forced retirement at a comparatively early age at a time when the life expectancy had increased by leaps and bounds. In addition to the reduced earnings period, the miserable stipend of a professor was hardly enough to meet modest daily needs. Thanks to the "American Society of Emeriti" the trustees of universities and of our hospitals will have finally seen the light, and the status of the emeritus professor as well as the manpower of the teaching profession will have benefited from making the emeritus a valuable asset to the teaching faculty. He will have become reactivated and will fill a high and important position. Because of his long experience, profound knowledge, and great diagnostic ability, he will have become a valuable asset and a wise consultant.

At the end of the new century one will wonder about the future of stomatology, just as today we wonder about the future of dentistry. Everyone will be puzzled as to what comes next. In addition, the third century will have brought new problems. Persons who have taken up residence in the recently opened areas on the moon will be confronted with conditions arising out of life in an artificial atmosphere, in which the climate and the food supply are a great handicap to the maintenance of a healthy body. We may, however, look forward to acquiring new knowledge from our colleges on Mars and other stars to combat these conditions. An "Interstellate Academy of Oral Pathology" will be founded, and the elected group of scientists will be expected to discover many new ideas useful to the stomatologist, the oral surgeon, and other specialists.

* * * *

When I awoke from this dream, I was glad to find myself still living in 1959 and en route to the A.D.A. Centennial Meeting. I had a good look into the future. I am sure that I have seen things which may never happen, although I am greatly impressed with the possibilities.

K. H. T.

OPERATIVE ORAL SURGERY

MYXOMA OF THE MANDIBLE, FOLLOWED BY RESECTION AND PROSTHETIC REPAIR

Report of a Case

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MYXOMAS of the jaws are rare and only a few cases have been reported.[1-5] Thoma and Goldman,[5] from their study of eleven cases, point out that myxomas of the jaws, unlike those of long bones which tend to recur and are often malignant, are benign tumors and are perhaps of odontogenic origin. On the basis of histologic evidence, they consider that myxomas of the jaws are in reality odontogenic fibromas which have undergone myxomatous degeneration. Thoma and Goldman have also pointed out striking association of these tumors with missing or embedded teeth, and they suggest that since these tumors rarely recur they should be enucleated. Resection of the jaws should be undertaken only if the tumor reaches large proportions and entirely destroys a portion of the jaws.

CASE REPORT

A 49-year-old Negro woman was referred to M. D. Anderson Hospital for treatment of a squamous-cell carcinoma of the cervix on June 8, 1956. An incidental finding was a mass in the right lower jaw which had been growing for approximately two years. The patient reported that a tumor had been resected in this area twelve years earlier, but she did not remember when the teeth were extracted. A nonsmoker, the patient did not use snuff or any other form of tobacco. Examination of the mouth showed the teeth to be in very poor condition. In the right lower jaw there was a large tumor mass approximately 5 cm. in diameter. This tumor was fungiform and was attached with its base to the mandible out of which it arose. There was no invasion of the floor of the mouth or cheek by the tumor (Figs. 1 to 4).

X-ray examination revealed a radiolucency with smoothly scalloped margins throughout the entire ramus on the right. This extended up into the ascending ramus and the

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Fig. 1.

Fig. 2.

Figs. 1 and 2.—Profile and lateral views of the face.

Fig. 3.

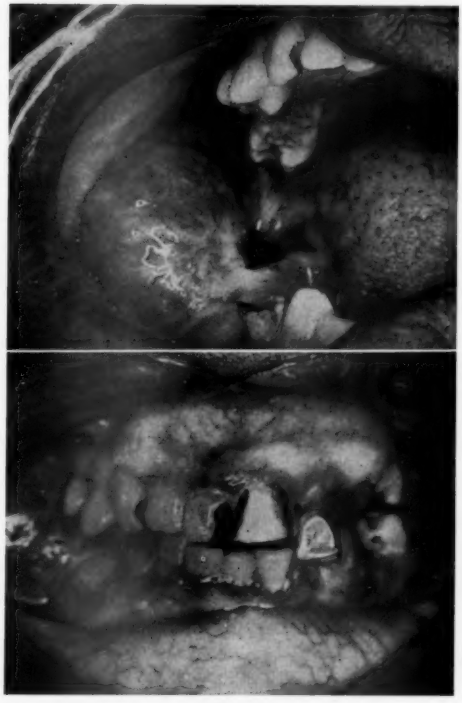


Fig. 4.

Figs. 3 and 4.—The tumor mass, which was fungiform and measured about 5 cm. in diameter. Note the indentation into the tumor caused by the upper teeth.

body, causing moderate expansion along the upper margin. On the basis of the history and clinical and roentgenographic findings, it was thought that the patient had an ameloblastoma of the right mandible (Figs. 5 and 6).

Fig. 5.

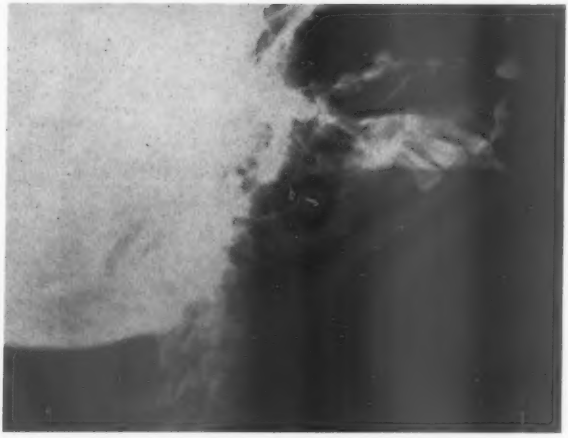


Fig. 6.

Figs. 5 and 6.—Roentgenograms showing anteroposterior and lateral views of the mandible. A large area of radiolucency with smoothly scalloped margins throughout the ramus and body of the mandible on the right and extending up to the premolar region on the left was noted.

Since the biopsy specimens on two occasions revealed chronic and subacute inflammation in subepithelial connective tissue and no tumor, and since the tumor was rather slow growing, it was decided not to do anything at this time but rather to attend

to the major and immediate problem for which the patient was referred to this hospital. The patient was seen in the gynecology clinic for treatment of squamous-cell carcinoma of the cervix. She had radiation to the pelvis followed by hysterectomy and lymphadenectomy.

Examination on Sept. 19, 1957, revealed no change in the tumor mass during the preceding fifteen months, but x-ray examination of the mandible disclosed a slight progression of the cystic lesion of the mandible, presumably an ameloblastoma. There was a further thinning of the cortex. Occlusal films indicated that the cystic lesion extended beyond the midline and to the region of the second premolar on the left.

Biopsy at this time was also negative. Therefore, the patient was tentatively scheduled for a resection of the mandible and possible prosthetic repair if frozen section reports were favorable.

Operation.—At the time of surgery, a large biopsy specimen was taken. Most of the tumor was removed by electrocoagulation and curettage. The frozen section report of the mass indicated myxoma. Because of the great extension of the tumor, it was felt that it would recur unless the mandible was resected.

A midline incision was made in the free lip, and the lip and cheek were reflected. The mandible was then divided on the premolar region on the left with a Gigli saw.

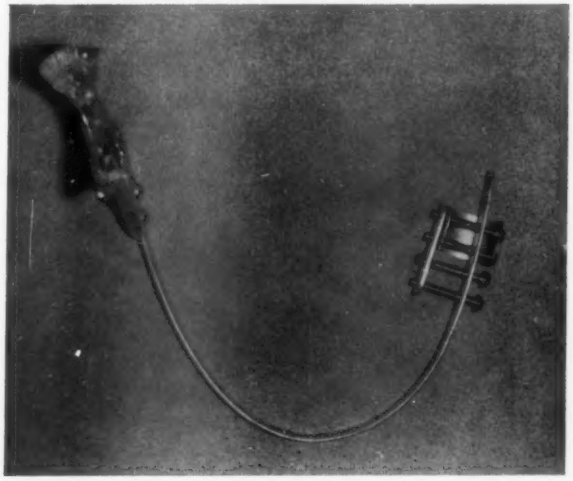


Fig. 7.—Cast-ticonium prosthesis; the head of the mandible was fabricated with methyl methacrylate.

The masseter, internal pterygoid, and temporalis muscles were detached with a periosteal elevator, and the temporomandibular joint was exposed on the right. A vertical incision was made in the capsule, which was reflected and separated by sharp dissection from the neck of the mandible. The horizontal ramus and the angle of the mandible were then avulsed from the temporomandibular joint and removed.

The wound was irrigated, and the defect created by the excision of the mandible was replaced by a previously designed cast-ticonium metal prosthesis. The fixation of the prosthesis was provided by drilling two holes through the bony mandible and securing the prosthesis with two stainless steel bolts and nuts. The condylar portion of the prosthesis was held in place by resuturing the joint capsule over the neck of the implant with several interrupted sutures. The oral cavity was closed, and the temporalis, internal pterygoid,

and masseter muscles were sutured to the appropriate perforation in the prosthesis. Soft tissues and skin were closed without tension over the prosthesis. A drain was inserted deep into the wound (Figs. 7 to 9).

A tracheostomy was then performed. The patient tolerated the procedure well and left the operating room in good condition. She received 500 c.c. of blood.

Postoperative Course.—This was uneventful, and the patient was discharged from the hospital in two weeks. The final pathologic report of the fixed specimen was myxoma (Fig. 10).

Fig. 8.

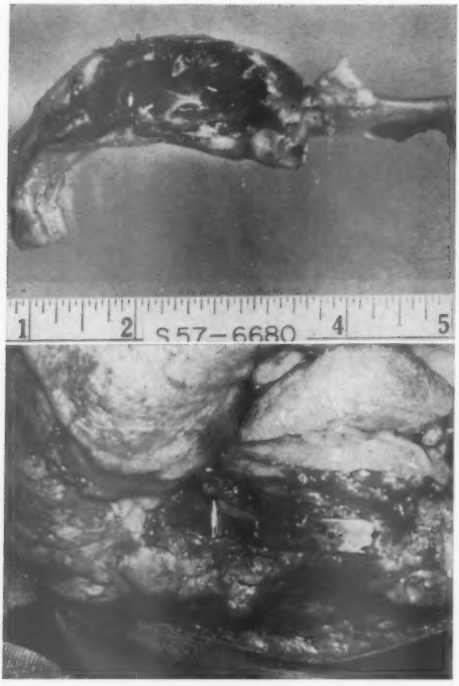


Fig. 9.

Fig. 8.—Resected mandible.
Fig. 9.—The ticonium prosthesis in place.

The patient was seen on Nov. 11, 1957, in the outpatient clinic, and roentgenographic examination revealed that the prosthesis was in good position. The left side of the mandible was normal, and the line of resection was smooth and did not demonstrate any abnormality (Figs. 11 and 12).

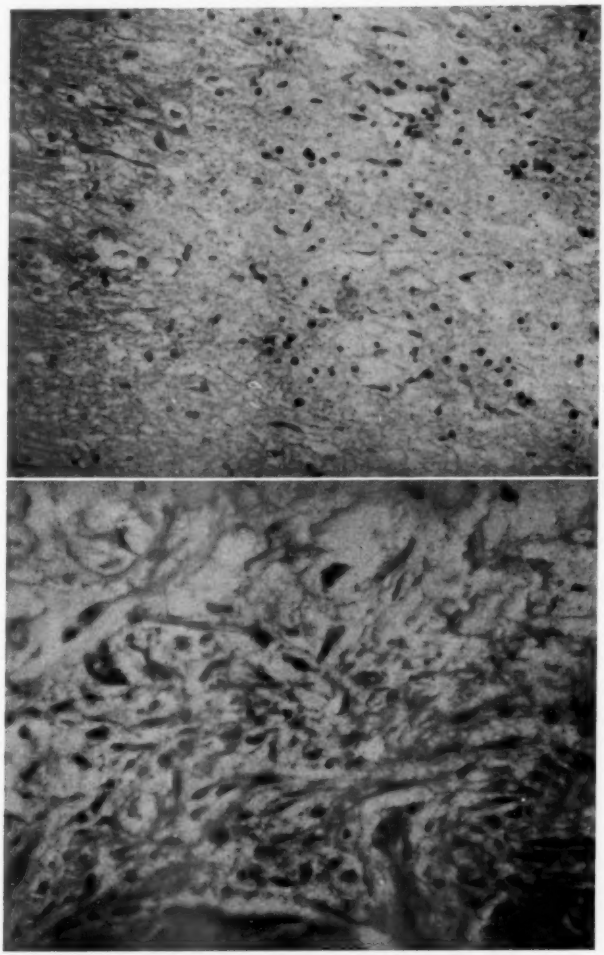
When the patient was last seen on May 18, 1958, nine months postoperatively, there was no evidence of residual or recurrent disease. The area inside the mouth and the incision outside the face healed well and there were good functional and esthetic results (Figs. 13 to 15).

SUMMARY

A case of myxoma of the mandible, treated by resection of the mandible and prosthetic repair, is reported. These tumors have the same roentgenographic

appearance as ameloblastomas, dental cysts, or giant-cell tumors, which should be given consideration in making a differential diagnosis. The final diagnosis should depend upon histologic examination.

A.



B.

Fig. 10.—Histologic examination of the resected specimen (myxoma).

Myxomas are best treated by either surgical curettage or surgical excision. The choice between a conservative surgical approach against a radical approach (namely, resection of the jaw) should depend upon the extension and the ease of enucleation of the tumor and the extent of bone destruction.

Fig. 11.

Fig. 12.

Figs. 11 and 12.—Roentgenograms showing the prosthesis in place.

Fig. 13.

Fig. 14.

Fig. 15.

Figs. 13, 14, and 15.—Note the nice esthetic and functional results. The areas inside the mouth and outside the face have healed well.

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OLFACTORY NEUROBLASTOMA

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INTRODUCTION

THE olfactory neuroblastoma, a most interesting but rare tumor of the nasal cavity and nasopharynx, is apparently of neural origin. In extremely rare cases it develops into the maxillary region and is of interest to the dentist. The case reported in this article is of interest because of the difficulty in diagnosis of an apparently quiescent, benign-appearing lesion and because of the unusual termination.

CASE REPORT

Present Illness.—The patient was first seen in the office on April 27, 1953, for consultation regarding an expansile swelling of the right maxillary premolar and molar area. An accurate history was not possible because of the low intelligence of the patient.

History.—The family said that the patient had been complaining of intermittent pain in the maxilla for about two years. Family history was noncontributory.

Physical Examination.—This was essentially normal except for the present condition.

Laboratory Findings.—Hematologic studies revealed a red blood count of 4,300,000; a white blood count of 4,500; hemoglobin, 88 per cent (13.5 Gm. per cent); cl. 1.08; coagulation time, 2 minutes; bleeding time, 1 minute 45 seconds.

Urinalysis findings were as follows: color, dark yellow; specific gravity, 1.032; acid (protein), negative; sugar, negative; acetone, negative; epithelial cells, occasional; mucus, 2 plus.

Roentgen Examination.—X-ray pictures of the right maxilla taken on April 29, 1953, revealed diminished bone density and apparent demineralization of the alveolar process, suggestive of osteomyelitis (Fig. 1).

Course.—The patient was admitted to the hospital on April 29, 1953, for biopsy and exploration.

Under Pentothal sodium anesthesia with nasotracheal intubation, an incision was made intraorally from the cuspid area distal to the malar tuberosity, exposing a bulging tumor mass. The tumor was firmly adherent and poorly differentiated from the environmental tissue

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and had invaded the maxillary sinus and floor of the nose. During removal of the tumor, hemorrhage was so slight as to be no problem. The area was then packed with plain 1 inch gauze, and the incision was closed with interrupted 000 black silk sutures.

The specimen varied in color from gray to brown, contained spicules of bone, and measured 6 by 5 by 4.5 cm.

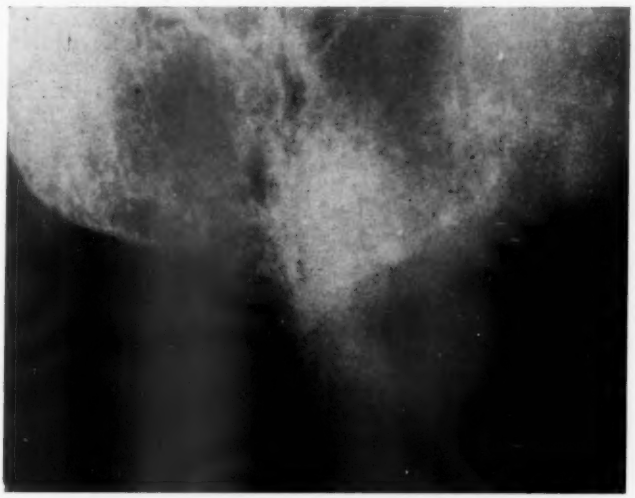

Fig. 1.—Intraoral occlusal film showing poorly defined areas of diminished bone density with apparent demineralization of the alveolar process.

Fig. 2. Fig. 3.

Figs. 2 and 3.—Extraoral extension of lesion, lymphomatous in appearance. Note involvement of nose, orbit, and upper lip.

Specimens were sent to four institutions for pathologic study. The findings were variously reported as (1) retinal anlage tumor, (2) melano-ameloblastoma (esthesioneuroblastoma of Portman, Bonnard, Moneau[1]), thought to arise from the olfactory area of the nasal mucosa, (3) undiagnosed malignant tumor of the maxilla of neural origin, and (4) an atypical adamantinoblastoma.

On Oct. 7, 1953, the patient underwent a radical excision of the right maxilla and partial excision of the left maxilla. The patient did very well postoperatively and by October 11 was discharged from the hospital. He was seen periodically in the next few months, and by June it was obvious that there was a recurrence in the area of the left maxillary sinus.

On July 2, 1954, the remainder of the left maxilla and all of the tissue that appeared malignant were removed. Again the patient did very well.

By February, 1955, it again became apparent that there was a spreading of the previous tumor (Figs. 2 and 3). At this time the patient refused further surgery. He appeared at the hospital on several occasions when spontaneous bleeding occurred, and he died on Aug. 4, 1955.

Fig. 4.—Appearance of extraoral lesion at autopsy. It involved both orbits, the entire nasal cavity, both sides of the maxilla, and the upper and lower lips.

An autopsy (Fig. 4) was performed and the tissues were again reviewed (Figs. 5, 6, and 7). Cellular detail of the first biopsy was identical with that taken at autopsy. The final diagnosis was olfactory neuroblastoma.

DISCUSSION

History.—According to Ash and Raum,[2] rare tumors of this type have been reported, largely in individual cases, as primary intranasal neuroblastoma, esthesioneurocytoma olfactif, esthesioneuroepithelioma olfactif, etc.

Berger and associates[3, 4] described the first case in 1924 and considered this tumor, which had features of both central nervous system and sympathetic nervous system neuroblastomas, to have its origin in the stem cell, the esthesioneuroblast of the olfactory placode. Other authors favor a source in the sympathetic elements of the nasal mucosa and possibly an origin in Jacobson's organ.

Anderson[5] believes these tumors to be of neural origin. They may be developmental, as an extrusion of brain element through a dehiscence in the

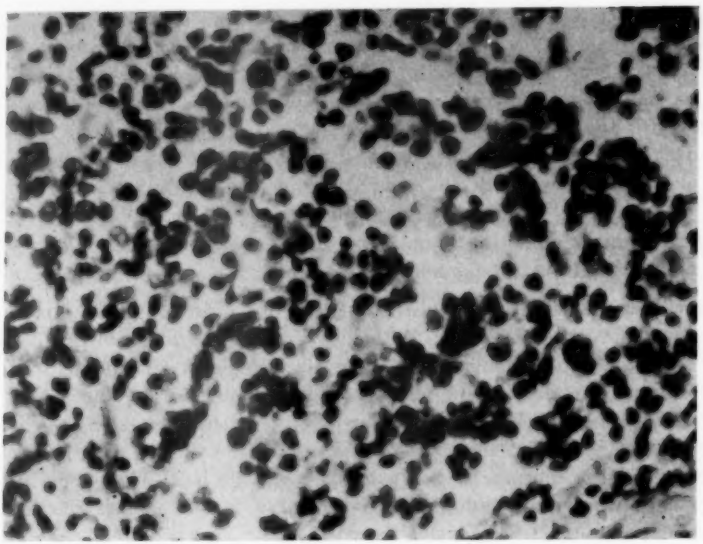

Fig. 5.—Note the confluent irregular masses of cells with scant cytoplasm and abundance of intercellular spaces. (Magnification, ×100.)

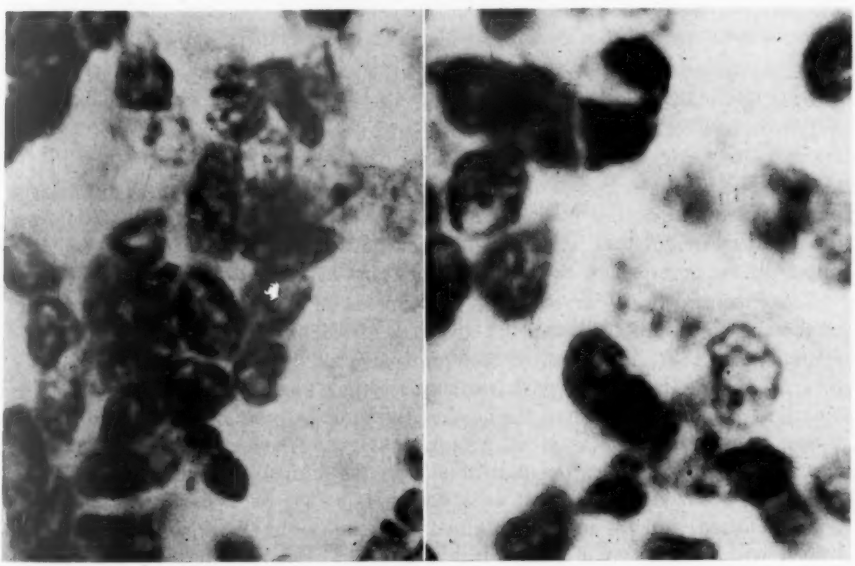

Fig. 6. Fig. 7.

Figs. 6 and 7.—Note the clumping of cells with scant cytoplasm and uniform nuclei, containing evenly dispersed chromatin in a delicate fibrillar network, prominent throughout the cells. In each cell there appears one or more prominent vacuole. (Magnification: Fig. 6, ×400, reduced ⅓; Fig. 7, ×600, reduced ⅓.)

Berger and Coutard[4] termed a like tumor "l'esthesioneurocytome olfactif," believing it to be a neoplasm showing differentiation only toward neurocytes and neurofibrils. Other authors have suggested an origin from sympathetic elements in the nasal mucosa.

cranial bones, and contain nerve cells and gliomatous elements. These may be present in the nasal cavity at the base of the nose. Other tumors arise from neural rests in the nose, especially at the site of the olfactory plaque. Neurofibromas, neurilemmomas, and other more complicated forms may arise from the nerves of the region as they do from other peripheral nerves. As a group, the neurogenous tumors in the nose and pharynx have a wide variety of histologic pictures. They may be sympathogonic, neurofibromatous, gliomatous, neurocellular, or an assortment of these elements.

Unlike reported neuroblastomas in other locations, which occur predominantly in children, these tumors occur in adults.

Incidence.—These tumors are extremely rare. Only one case is on file at the Armed Forces Institute of Pathology in Washington, D. C. It is listed as an esthesioneuroepithelioma olfactory, accession No. 733214, with a history as follows: A female patient, 56 years old, had no nose trouble until recently and had spots before the eyes, poor hearing, and loss of sense of smell. There was no obstruction of breathing. X-ray examination showed a mass on one side, indicating a large fibroma or polyp. There was no bone erosion or ulceration. The first specimen was thought to be a polyp. The patient returned three months later with more extensive growth. As complete a removal as possible was done in February, 1950. She had external irradiation, about 4,100 r. In 1950 the tumor involved the antrum and ethmoidal labyrinth. After its removal, 400 mg. of radiation was inserted in the area. By February, 1952, there had been no recurrence of the growth.

Embryogenesis.—To develop the possible faults that might justify these ectopic growths being in the maxilla, one must review the embryological sequences of development of the face and olfactory system.

Streeter[6] states that before the 7 to 8 mm. stage, the neural tube, by its massiveness, is the prime determiner of the form of the embryo. The olfactory plate appears to induce changes in the adjacent mesenchyme, and, aside from the small rudiment that will form the maxilla, there is nothing to represent the upper lip or nose except the two olfactory pits at the 7 to 8 mm. stage.

At horizon 16 (9 to 10 mm.) the increasing breadth of the brain determines the considerable distance between the two olfactory pits, since they lie ventrolateral to it. The roof of the mouth slopes forward between the olfactory pits as a smooth surface with no interruption to mark the location of the maxilla. The mesenchyme of the head at this time is by no means a homogeneous tissue. Instead, it contains cell groups that come from more than one source and that have different potentialities. In the human embryos the cytologic difference between neural crest cells and cells of the surrounding mesenchyme is less marked, and the migration and fate of individual crest cells has not been traced with certainty. From their initial lateral position the two sides of the cranium gradually spread by interstitial growth, enlarging and increasing dorsalward, and finally come together over the dorsal surface of the head. The right and left maxillary fields are, however, still widely separated. Between them is the broad region that is to become the roof of the mouth. The only surface

markings of this region are two rounded, low elevations constituting the primordia of the primary palate (premaxillary, intermaxillary, or incisive bone). Aside from these modest representatives, there is lacking any upper jaw. In many respects the ventral part of the cranium and the floor of the mouth is more advanced than its sides and top. At horizon 17 (11 to 13.6 mm.) transformations of the right and left olfactory pits lead to the establishment of bilateral respiratory passages which bypass the mouth. Except for that maintained by the nasal fin, the continuity between the nasal sac and the roof of the mouth becomes interrupted by the act of proliferation of the mesenchyme of the premaxillary and the maxillary growth centers, which blends across from one center to the other in front of the nasal fin. The primary palate makes its appearance, and the nasal fin becomes transformed from an epithelial plate to an epithelium-lined passage.

At horizon 18 (14.5 to 16 mm. stage, 37 days) the ethmoid and maxillary epithelium are better defined. Communication between the respiratory tract and surface of the face that bypasses the mouth is established, and the nasal passages are better defined. At this stage the olfactory nerve is developing between the future nasal septum and the ethmoidal epithelium and dorsal to the vomeronasal organ (Jacobson's organ). The olfactory epithelium moves dorsally with development of the respiratory bypass, and the olfactory evagination of the brain becomes prominent.

From these embryological sequences, it can be seen that cells making up the olfactory system are adjacent to the future maxilla and can be displaced or left behind during development of the maxillary region. There may be a continual line of cells (neural crest cells) from the maxillary region extending up to and including the olfactory plate as the olfactory membrane is carried cranially and the nose and maxilla develop in more detail. Future interruption of cell activity in these areas, for any apparent reason, may stimulate proliferation. These tumors may then develop from dormant cells already in the area or from cells in the olfactory membrane and expand to fill the maxillary sinuses.

Clinical Features.—Clinical features of this tumor are indistinct. Swelling and pain may be present and may persist over the area. Nasal tumors usually appear as firm, obstructive, polypoid masses with attachments high in the nasal cavity, usually in the region of the olfactory mucous membrane.

Roentgenographic Features.—Diagnosis of these lesions from x-ray findings alone is not reliable. Outlines of these tumors are not visible, as definite boundaries are not present. The lesions may reveal decreased bone density and areas of demineralization, and they may be mistaken for osteomyelitis. X-ray examination must remain nondiagnostic of this type of tumor.

Diagnosis.—Diagnosis of this tumor is by histologic examination of representative tissue.

Differential Diagnosis.—

Neurogenic tumors: According to Ash and Raum,[2] the majority arise in the roof of the nose, but these tumors are also found in the nasopharynx. There

are two types: (1) one that develops from peripheral neural elements and belongs to the peripheral neurilemmomas or ganglioneuromas found in association with peripheral nerves elsewhere and (2) those of central or neural crest origin. The former contains, in varying proportions, neurofibrous and neurilemmal and nerve-cell elements. Its histologic character, therefore, varies greatly and confusingly in different tumors. In one, the neurilemmal element will predominate, including the typical palisading of cells, and its identity is evident. In others, the ganglion cells are the prominent feature, and in its more primitive form its identity may not be clear. Another category of lesions, not really tumors, is the result of maldevelopment. Here a portion of the frontal lobe may escape through a defect in the cribriform plate or through the ethmoidal sutures and appear in the nose or subcutaneously at the base of the nose. Such "tumors" are readily recognized histologically, for they retain the brain cortex element. These may be apparent at birth because of the external deformity at the base of the nose or the nasal polyp.

Retinal anlage tumors: Tissues described by Clark and Parsons,[7] and Martin and Foote[8] involve the maxillas of infants. In the melanin, epithelial-like cells of variable shape, neurocytes, and spindle cells are the cellular elements of this neoplasm which develops in misplaced optic remnants. The spindle cells are perhaps still undifferentiated smooth muscle fibers. The so-called "melano-ameloblastomas" are probably tumors of retinal anlage.

Ganglioneuroma—peripheral: This tumor originates either from a sympathetic chain ganglion or from displaced primordial elements of a sympathetic or spinal ganglion. Its elements are possibly derived from the neural crest or the neural tube. The presence of large nerve cells of the pseudounipolar type and of bundles of nonmedullated nerve fibers, with neuroectodermal supporting elements (cells of Schwann, capsule cells), characterize this tumor which occurs only in the peripheral nervous system.

Spongioneuroblastoma, glioneuroma: These tumors relate to the central nervous system.

Neuroectodermal tumors: These tumors are not discussed here. For a detailed account, the reader is referred to the excellent paper by Kuhlenbeck and Haymaker.[9]

Complications.—Olfactory neuroblastomas tend to grow by expansion. They invade and eventually erode, involving the bony cavities with persistence, and they may impede vital functions. They tend to recur locally but not to metastasize.

Treatment.—These tumors are treated by surgery, irradiation, or a combination of both.

Prognosis.—These neurogenic tumors behave clinically about the same as other tumors of the nose and paranasal sinuses. They rarely metastasize, and if the tumor is removed locally and no vital functions are impaired the prognosis is good. Impairment of vital functions may place the patient's life in danger.

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AMERICAN DENTAL ASSOCIATION 100 YEARS 1859 · 1959

A LARGE PERIODONTAL CYST OF THE MANDIBLE

A. Norman Cranin, D.D.S., and Samuel L. Cranin, D.D.S.,** Brooklyn, N. Y.*

THE periodontal or radicular cyst generally forms at the root area, most often at the apex. Its origin is usually infectious in nature, and the developmental pattern evolves from an epitheliated granuloma. First, a central cavity forms; this is subsequently lined with epithelium and then tends to grow on the surfaces.[1] Residual periodontal cysts are quite common and often are found in edentulous jaws. The case reported in this article involved an extremely large cyst of this type.

CASE REPORT

A 72-year-old well-developed, well-nourished male carpenter had a large, discrete, unilocular cyst of the mandible. His chief complaint was inability to wear his lower denture.

Present Illness.—Four months prior to the time he was referred to us, the patient reported that he was unable to chew. His dentist constructed a new lower dental prosthesis for him. This served satisfactorily for three and one-half months; then the patient returned with the same complaint. The dentist made a careful examination, took several intraoral roentgenograms, and told the patient that he had found a growthlike process in his jaw. A consultation was arranged.

Past History.—No history of a fall or blow could be elicited from the patient. He did not remember having had any operation or unusual or difficult extraction in the region of the anterior mandible. Both the past medical history and a systemic review were noncontributory. The patient's last remaining teeth had been extracted fifteen years earlier.

Regional Examination.—The patient had an obviously enlarged chin (Fig. 1). Otherwise, his facies, color, and general appearance were normal. He was edentulous. It was noted that the tongue was forced upward and backward and that the entire floor of the mouth was obliterated by a hard, expanded mass. Palpation revealed evidence of an expanded cortical plate which was crepitant and eggshell-like. This occupied the entire anterior part of the mandible, from mental foramen to mental foramen. It extended on the lingual aspect to a point which caused it to eliminate the lingual curvature. Superiorly, it bulged the crest of the ridge about 0.5 cm. Labially, it was pronounced enough to cause facial disfigurement. The overlying mucous membranes were pink, moist, and healthy. There were no enlarged or tender lymph nodes in the neck. Besides his inability to chew or to retain his lower denture, the patient had recently experienced speech difficulties. Otherwise, he had no complaints. His appetite was excellent, and he had not suffered weight loss or other debilities. No paresthesia was noted.

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**Associate Attending Dentist, Unity Hospital, Brooklyn, New York.

Roentgenologic Examination.—Anteroposterior, lateral oblique (Fig. 2), and occlusal (Fig. 3) films revealed a large monolocular, clearly defined radiolucency. This appeared to encompass the left mental foramen, and no sign of this structure was in evidence. All

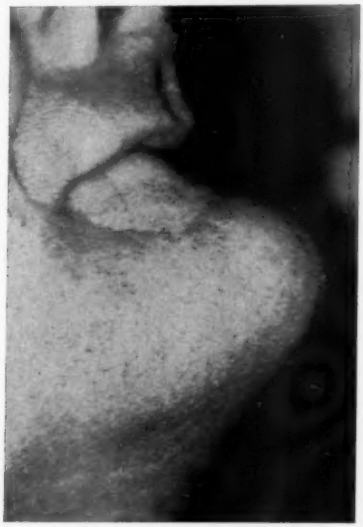


Fig. 1.—Preoperative photograph of patient showing enlargement of chin.

Fig. 2.—Right lateral roentgenogram.

of the cortical plates were thinned and expanded. The inferior border of the mandible appeared to be barely thick enough to prevent pathologic fracture if an operation were attempted. (However, in these cases there is generally adequate bone lingually or labially to prevent such an accident.)

Our impression was that this was a residual follicular or radicular cyst. The possibility of ameloblastoma could not be ruled out.

Surgical intervention was clearly indicated. The lesion appeared to be in a dynamic state of expansive growth. The question of whether to marsupialize the area or to attempt complete enucleation presented a problem. The advantages of the conservative Partsch operation were (1) elimination of the danger of fracturing the jaw and (2) shortness of operating time, allowing the operation to be performed in the office under local anesthesia. The disadvantages of marsupialization were (1) the necessity of leaving pathologic tissue (the cyst membrane) in the bone[1] which, in case the lesion turned out to be an ameloblastoma, might be the cause of recurrence; (2) the fact that healing would consume a great deal of time and require constant postoperative care; and (3) the long period of time that would elapse before the patient could be rehabilitated prosthetically.

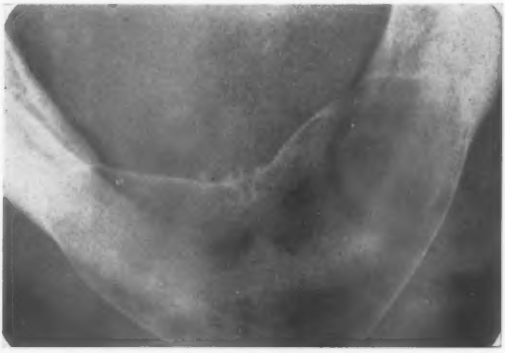
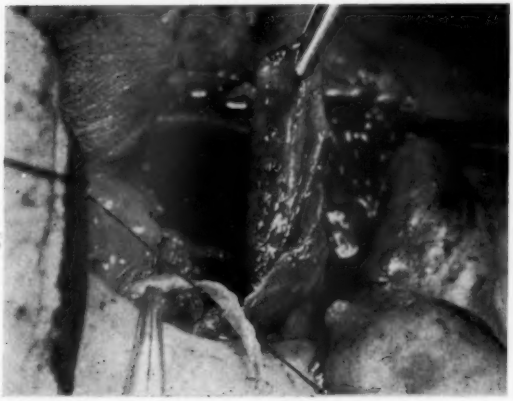


Fig. 3.—Occlusal film showing large radiolucency in region of left mental foramen.

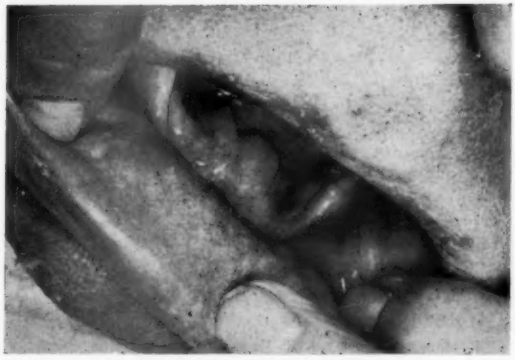
The advantages and disadvantages of complete enucleation were about the opposite of the factors just listed with respect to marsupialization. Although the patient was rather aged, his physical condition was excellent. Both operator and patient were anxious for rapid healing, and it was considered essential that the patient's nutritional status be maintained rigidly because of his age. In order that prosthetic rehabilitation might be hastened and the postoperative course minimized, it was decided[2] that complete enucleation should be performed. The patient was informed of the possibility of pathologic fracture, and his dentures were prepared with fixation wires in case it became necessary to use them for fracture fixation. The patient was admitted to the Madison Park Hospital of Adelphi College in December, 1957.

Operation.—Following induction of thiopental sodium and nitrous oxide-oxygen nasotracheal anesthesia, an incision was made from molar area to molar area on the crest of the mandibular ridge. Labiolingual mucoperiosteal reflection was extremely difficult, and no clear periosteal layer was evident. The underlying bone was a fraction of a millimeter in thickness and was picked away with dissecting forceps. During this procedure, accidental puncture of the heavy cyst membrane caused the escape of about 50 ml. of heavy, brown-colored fluid with cholesterol crystals. Enlargement of the bony perforation made possible the enucleation of most of the leathery membrane in several large fragments (Fig. 4, *A*). This was followed by removal of labial and lingual walls because of their expansive shape and dangerous thinness. The walls were reduced to their lower junction with the inferior border of the mandible. Only the inferior portion of the defect was permitted to remain (Fig. 4, *B*). This was about 1 mm. thick and 15 mm. deep labiolingually. Although the



A.

B.



C.

Fig. 4.—*A*, Enucleation. *B*, Bony defect. *C*, Thirteen weeks postoperatively.

two posterior portions of the horizontal rami could be rotated, permitting movement in the cyst area, the concave shape of the defect made it architecturally stronger than its dimensions seemed to indicate. After the membrane in the distal sections was removed, the mental neurovascular bundles could be identified and these were preserved painstakingly. Both mental foramina had been destroyed by the lesion, but their contents appeared to be intact. A survey of the operative region at this juncture revealed that, because of the removal of the lingual bony wall, the lingual adnexa had prolapsed into the wound. To correct this, two through-and-through silk sutures were placed over the sublingual glands on either side and were drawn through the floor of the mouth to emerge from the submandibular skin, where they were tied around cotton rolls. The labial and lingual mucoperiosteum was laid into the defect, and closure was made with interrupted silk sutures, after which 23 inches of sterile petrolatum packing was placed into the defect. The chin was dressed with sterile pressure packing, and the patient was returned to his room fully reacted.

Fig. 5.—The prosthesis.

Postoperative Course.—The patient was catheterized, and ice packs were applied to the face and neck areas. He received 3,000 c.c. of saline, 5 per cent dextrose and water, soluble protein, and alcohol intravenously for three days. His pain was minimal and was readily controlled. Edema was not marked. Nasal feeding was employed for the next two days. Because of the patient's complaints, it was decided that he should be ambulatory and that he should be fed by mouth. His recovery was rapid from this point on. The packing was shortened on the fifth postoperative day, and 4 inches was removed every second day thereafter. The patient irrigated the wound with hydrogen peroxide 3 per cent and sterile water every hour. On the eighth day sutures were removed without noticeable lingual prolapse. Antibiotic therapy was discontinued on the fourteenth day; the drain was completely removed by the eighteenth day and was replaced with a much shorter length. After receiving careful postoperative instructions as to diet and vitamin supplementation, lavage, and other supportive measures, the patient was discharged on the nineteenth postoperative day. Further dressings, roentgenographic examinations, and irrigations were performed in the office. Healing was rapid, and in six weeks the entire defect was well lined with a healthy-appearing mucous membrane. Only 8 inches of petrolatum gauze would fit into the area. In eight weeks all signs of right-sided paresthesia had disappeared. By the end of ten weeks no packing could be introduced, and all undercuts had rounded out and filled in. Within thirteen weeks full sensation had returned on the left side (Fig. 4, *C*). A prosthetic appliance (Fig. 5) was constructed by one of us (S. L. C.) during the sixteenth week; with this, the patient has been able to function satisfactorily (Fig. 6). The postoperative roentgenogram was satisfactory (Fig. 7).

*Pathologist's Report.**—The specimen consisted of a heavy-walled cystic membrane with stratified squamous epithelium, a muscular layer, and some islets of cortical bone. The cyst wall showed infiltration of round cells and downgrowth of rete pegs. *Impression:* Radicular cyst.

Fig. 6.—Postoperative photograph of patient.

Fig. 7.—Postoperative roentgenogram of left side of mandible.

DISCUSSION

The advantages of complete enucleation were weighed, and this procedure was chosen despite the obvious risks. Results were gratifying in view of the rapid healing, the short postoperative period, the promptness of the patient's rehabilitation, and the complete removal of pathologic tissue. Had a fracture occurred, the surgeon was prepared to use circumferential wiring, with both dentures employed for fixation.

*Dr. Lester R. Cahn, Oral Pathologist, Mount Sinai Hospital, New York, New York.

SUMMARY

The case of a large mandibular cyst in a 72-year-old edentulous man has been presented. Diagnosis, management, and postoperative care have been described.

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AMELOBLASTOMA OF SYMPHYSIS OF MANDIBLE

Report of a Case

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History.—Patient E. Z., a 51-year-old man, had his six remaining mandibular anterior teeth extracted in the office of a local oral surgeon. It should be noted that this procedure was done without preoperative radiographs. The postoperative course was uneventful. Approximately three years later the patient went to see his family dentist for extraction of his remaining maxillary teeth and the construction of a full upper and lower denture. During the routine preprosthetic examination, the dentist noticed a swelling in the anterior part of the mandible. Upon digital pressure, a milky fluid was expelled from this area. Routine intraoral radiographs were taken and the patient was referred to me.

Fig. 1.—Circular opening into cavity collected food and debris, a source of irritation to the patient.

Oral Examination.—In the expanded symphysis of the edentulous mandible, there was a circular opening into a cavity which collected food and debris and served as a source of irritation (Fig. 1). The area of labial expansion extended from the region of the right cuspid to the left cuspid. The cortical plate was thinned and was easily compressed.

*Professor of Oral Surgery, School of Dentistry, University of Pittsburgh.

Fig. 2.—Radiographic appearance of ameloblastoma.

Fig. 3.—*(For legend, see opposite page.)*

Roentgenographic Examination.—Roentgenograms revealed a large multilocular cystic area of the symphysis of the mandible. The labial cortical plate is expanded and thinned. In the left cuspid and premolar area there was a thinning and expansion of the lingual cortical plate. There were many small cystic areas in or around the larger cystlike areas. This lesion had the radiographic appearance of an ameloblastoma (Figs. 2-5).

Fig. 4.

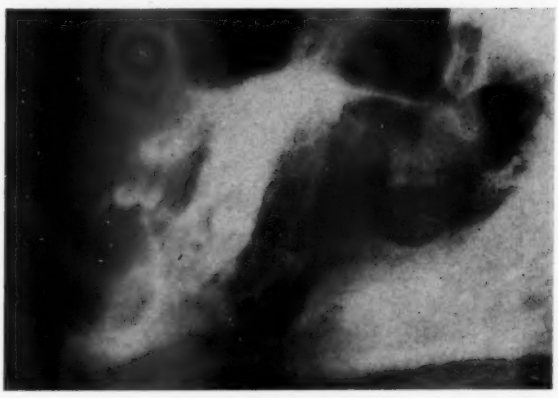

Fig. 5.

Figs. 3, 4, and 5.—Radiographic appearance of ameloblastoma.

The patient was admitted to my service at the Eye and Ear Hospital, Pittsburgh, Pennsylvania, on May 30, 1955.

Physical Examination.—The routine medical history and physical examination revealed no systemic disease.

A biopsy was performed, and the diagnosis was "ameloblastoma of the mandible with chronic inflammation and reactive hyperplasia."

Operative Notes.—On May 31, 1955, under Pentothal sodium and endotracheal nitrous oxide and oxygen anesthesia, an incision was made in the mandible, extending from the second premolar on the right to the second premolar on the left. The tissue was reflected on both the lingual and the labial

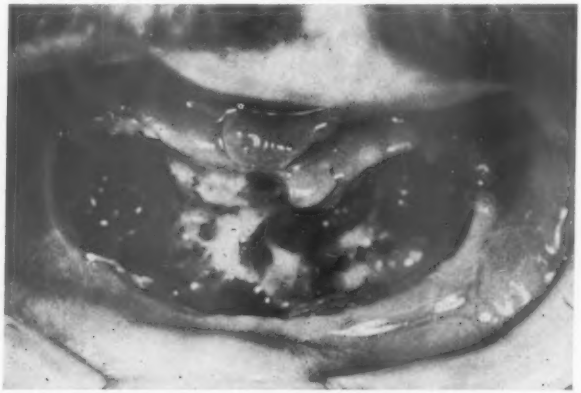

Fig. 6.—The wound when dressing was removed ten days postoperatively.

Fig. 7.—Large lobules of pyogenic granulation tissue (eight weeks after operation) covering loose sequestrum.

surfaces. In spite of the large size of this tumor, a conservative approach was decided upon in order to preserve the continuity of the mandible. I planned to excise the tumor with a reasonable amount of bone beyond the periphery, including the labial and lingual cortical bone, and leave only the inferior border of the mandible. This was accomplished after the expanded bone overlying the tumor was exposed by the reflection of large mucoperiosteal flaps labially and lingually by means of burs, chisels, and rongeurs. The inferior alveolar canal

was cut through bilaterally; bleeding was controlled by coagulation and packing. To destroy any tumor tissue which might have invaded the cancellations beyond the area excised, the surgical site was thoroughly coagulated with a ball coagulating tip. The cavity was then filled with iodoform gauze saturated

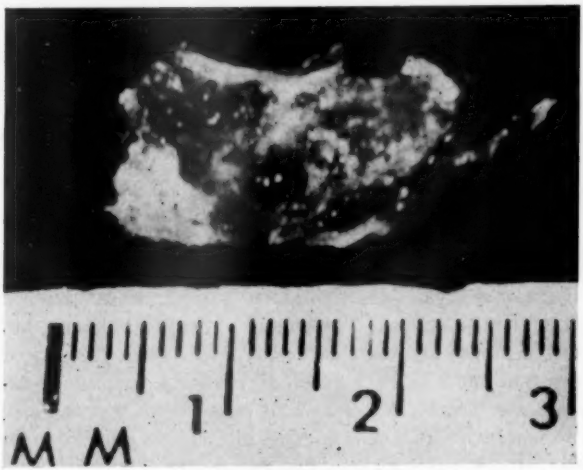

Fig. 8.—Sequestrum which was removed.

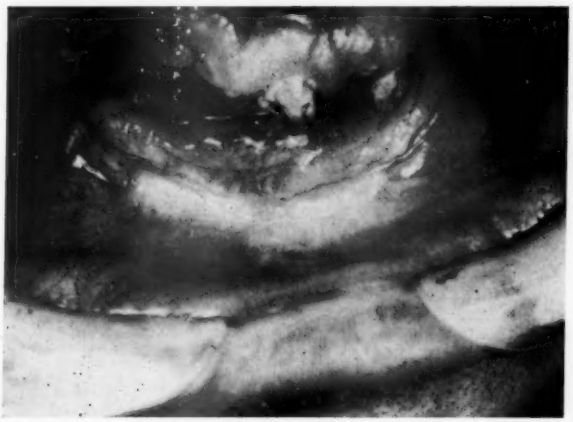

Fig. 9.—Clinical appearance one year later.

with Carnoy's solution. The gauze was held in position by sutures passed over the packing and through the labial and lingual soft tissue flaps. The patient left the operating room in satisfactory condition.

Pathology Report.—The specimen consisted of ten pieces of moderately firm, irregularly shaped, grayish tan tissue submitted in formalin. Portions of

each tissue were covered by opaque, tannish white, somewhat granular membrane, and attached to many of the pieces were large fragments of bone. In aggregate, this specimen measured 7 by 5 by 2.5 cm. The cut surface of most of the fragments was pale tannish white, smooth, and somewhat granular.

Microscopic examination of a section showed the tumor to be composed of a dense fibrous connective tissue lined by stratified squamous epithelium with marked acanthosis. Within the connective tissue were large sheets and columns of epithelium of epidermoid type and areas of basal cells which encircled groups of large vacuolated cells connected by cytoplasmic bridges. There were scattered areas of lymphocytic and polymorphonuclear leukocyte infiltration. Bony trabeculae were seen surrounding the tumor mass.

Dr. R. S. Totten, pathologist, returned a diagnosis of ameloblastoma of the mandible.

Postoperative Course.—The postoperative course was satisfactory, and the patient was discharged from the hospital on June 2, 1955. He was to receive follow-up treatment in the office. The wound appeared as shown in Fig. 6 when the dressing was removed ten days after the operation. Eight weeks after the operation the wound had large lobules of pyogenic granulation tissue in it, covering a loose sequestrum (Fig. 7). This sequestrum was the anticipated end result of the extensive coagulation carried out at the time of operation. The sequestrum was removed (Fig. 8). The wound now epithelized rapidly and healed well.

Follow-up.—Two years later, there is no visual or radiographic evidence of a recurrence of the tumor (Fig. 9). The mandible will be radiographed annually for the next five years in order that any radiographic evidence of recurrence might be discovered early.

EXODONTIA

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THE RELATIONSHIP OF THE ROOTS OF MANDIBULAR THIRD MOLARS TO THE INFERIOR DENTAL CANAL

C. R. Stockdale, L.D.S. (Manc.), F.D.S.R.C.S. (Eng.), Manchester, England

ALTHOUGH trauma to the inferior dental nerve following the removal of mandibular third molars has been reported in the literature, it is suggested that trauma to this nerve is more common than is realized. Suggested explanations of why it is not more frequently recognized are the possible lack of follow-up by the dental surgeon and the patient's failure to report any sensory disturbances, especially in mild cases. The trauma is usually the result of the intimate relationship, in many cases, of the roots of the mandibular third molar to the inferior dental canal and its contents.

It is my intention in this article to explain how an anatomic relationship of the roots of the mandibular third molar to the inferior dental canal develops, the diagnosis of this relationship, the traumatic injury to the canal and its contents which is likely to occur following removal of mandibular third molars, and finally precautions to minimize the possibility of such injuries are discussed.

To ascertain the frequency of the relationship of the roots of lower third molars to the inferior dental canal, records were kept of 100 consecutive cases in which mandibular third molars were extracted under continuous nitrous oxide-oxygen anesthesia. Their state of eruption and their relationship to the canal, as diagnosed radiographically and by macroscopic examination of the roots after the removal of the teeth for grooving by the canal, were noted. The patients were also closely "followed up" so that any untoward sequelae could be noted. Of these teeth, 13 per cent were unerupted, 20 per cent were partially erupted, and 67 per cent were clinically fully erupted. Of the unerupted teeth, 100 per cent were related to the inferior dental canal of the partially erupted teeth, 55 per cent were related to the inferior dental canal of the erupted teeth, and only 5 per cent were related to the inferior dental canal.

Of the unerupted teeth, 23 per cent of those removed produced such postoperative sequelae as anesthesia, paresthesia, postoperative pain of an

obscure nature, and hemorrhage along the canal. Of the partially erupted teeth, 10 per cent of those removed manifested postoperative sequelae suggestive of damage to the inferior dental canal.

To understand how a relationship between the roots of a lower third molar and the inferior dental canal occurs, a knowledge of the developmental anatomy of the mandible (particularly the inferior dental canal) and the developing third mandibular molar is necessary. In the following discussion, as indeed throughout this article, it is assumed that no such factors as abnormal nutritional, endocrinologic conditions, or osteodystrophies of the jaws are present.

POSITION OF THE INFERIOR DENTAL CANAL IN THE DEVELOPING MANDIBLE

Radiographic examination and dissections of the mandible in infants reveal the inferior dental canal lying near the lower border of the body of the mandible (Figs. 1 and 2). Even at the age of 7 to 8 years, the canal is not far removed from the lower border.

Fig. 1.—Dissection of mandible of child about 3 years old showing close relationship of the developing permanent molars of the inferior dental canal.

With increase in age, the distance between the canal and the lower border of the mandible becomes greater. This is not due to any upward movements of the canal but is the result of the deposition of bone at the lower border of the mandible which occurs during the development of the mandible from the infantile to the more adult state. This growth occupies the first seven years of life.

The mandibular foramen in the mandible of a child is in a position relative to that in the adult, that is, it is in approximately the midpoint anteroposteriorly and at a level just above the occlusal plane of the mandibular teeth opposite the point of greatest concavity of the external oblique ridge of the ascending ramus. The mandibular foramen maintains this relative position throughout the growth of the mandible.

There is an increase in the over-all length of the mandible (condyle-gnathion distance) due to interstitial condylar growth, as well as a "backward" movement of the ascending ramus resulting from bone absorption along the anterior border and bone deposition along the posterior border (so increasing the length of the horizontal ramus of the mandible, as to accommodate the permanent molars as they erupt). Concurrently, there is an upward and backward movement of the mandibular foramen, together with the mandibular canal, in order that the mandibular foramen might maintain its constant position. This is achieved by the progressive deposition of the bone at the sharp anterior border of the foramen and simultaneous absorption of bone on the medial aspect of the ramus behind this.

As the mandibular foramen moves "backward," the mandibular canal must do likewise in its course in the ascending ramus. Failing this, the bone absorption at the anterior border of the ascending ramus would result in the canal lying near the anterior border in the adult mandible.

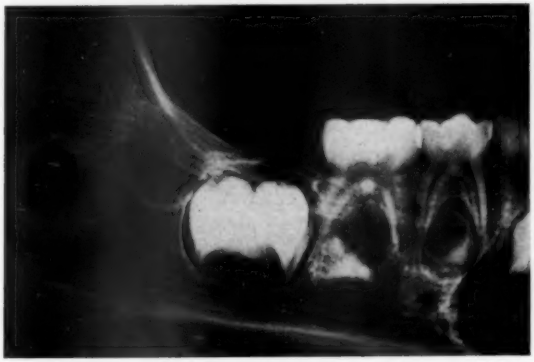

Fig. 2.—Roentgenogram of mandible of a child about 3 years old.

RELATIONSHIP OF THE DEVELOPING PERMANENT MOLARS TO THE INFERIOR DENTAL CANAL

The crypts of all the developing permanent molars are, in their earliest stages, intimately related to the roof of the inferior dental canal (Fig. 1). As development and calcification of the roots of the first permanent molar take place, the tooth moves in an upward direction so that the apices come to be at some distance above the canal. This distance increases as eruption proceeds, and when the tooth comes into clinical occlusion there is no relationship of its apices with the canal.

The apices of the second permanent molar maintain a longer relationship to the mandibular canal than do those of the first permanent molar. By the time it is in occlusion and the roots fully formed, however, there is an appreciable distance between its apices and the canal.

Similarly, the lower third molar commences its development in close relation to the canal but moves away as development proceeds. When the tooth is in its normal clinical position, the apices are normally not in relation to the inferior dental canal, although the distance between the apices and canal is less than in the case of the first and second molars.

In normal mandibular development, absorption of the anterior border of the ascending ramus of the mandible together with a forward movement of the erupted teeth creates space in the retromolar region, allowing growth of the alveolar bone and eruption of the mandibular third molar into its normal position. Adequate bone space will have been created above the inferior dental canal by the vertical growth of alveolar bone for normal root development to take place, so that when development is completed the apices of the lower third molar come to lie some distance above the canal.

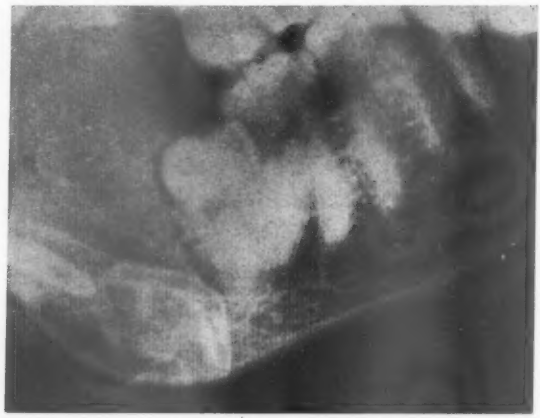

Fig. 3.—Vertical impaction of a lower third molar with a resultant relationship of the apical third of the root to the inferior dental canal.

If, however, mandibular growth is such that not enough space is created for the eruption of the lower third molar, normal eruption of this tooth will be prevented and an impaction will result. The tooth is prevented from moving in an occlusal direction; therefore, the roots develop in a downward direction and may become related to the inferior dental canal (Fig. 3). From evidence obtained from extracted mandibular third molars and the examination of radiographs, it is obvious that the compact bone of the walls of the canal, together with its contents, are not deflected by the developing roots of the lower third molar but that in the precalcification stage the growing soft cellular structures of the roots seek an easier growing course and are deflected by the canal. They may grow in close proximity to the roof of the inferior dental canal deflected to the buccal or lingual side or to both sides, or they may completely surround the canal.

Relationship of the roots of the mandibular third molar to the inferior dental canal is also determined by the height of the body of the mandible and also the length of the roots of the third molar. These are controlled by hereditary factors.

Fig. 4.—Occlusal view of mandible showing "mandibular tuberosity."

Fig. 5.—Occlusal roentgenogram of mandible with silver probe inserted in the inferior dental canal showing the lateral relationship of this canal to the molar teeth.

BUCCOLINGUAL RELATIONSHIP OF THE INFERIOR DENTAL CANAL TO THE ROOTS OF THE MANDIBULAR THIRD MOLAR

Sicher[2] states that the mandibular canal usually lies medial to the roots of the mandibular third molar and is only rarely found on the lateral aspect. He explains this by the fact that the mandibular third molar is lingually inclined and, therefore, its roots pass over the canal.

On the other hand, Cogswell[1] states that the canal lies to the lateral side of the roots, and if the tooth has a lingual inclination the root apices may contact, straddle, or cross the canal. He supports this view by pointing out that the

ascending ramus is "flared-out" at the angle to the body of the mandible (when seen from above) and that there is more buccal than lingual bone in the third molar region, the third molar occupying what might be termed a "mandibular tuberosity" (Fig. 4). Accordingly, the canal starts laterally in the ascending ramus and maintains this lateral relationship to the roots of the mandibular third molar in the body of the mandible (Fig. 5).

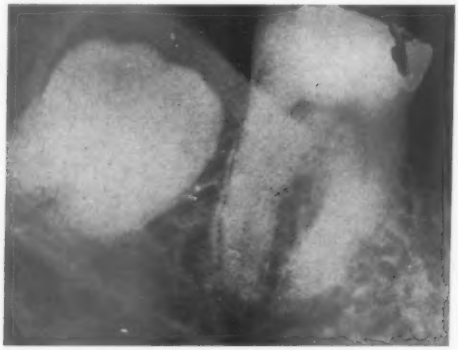

Fig. 6.—Roentgenogram of a lingually inclined lower third molar, the inferior dental canal lying on the medial aspects of the roots of this tooth.

Fig. 7.

Fig. 8.

Fig. 7.—Grooving on the inferior surface of the roots of a lower third molar.
Fig. 8.—Grooving on the lateral aspect of the roots of a vertically impacted lower third molar.

In the majority of cases that I have observed the canal has been placed lateral to the roots of the mandibular third molar, and only in cases where there has been marked lingual inclination of the tooth has the canal been found on the medial aspect of the roots as indicated by grooving on the lingual surface of the root (Fig. 6).

The relationship of the roots of the mandibular third molar to the inferior dental canal may be said to be variable and may be broadly classified as follows:

(1) *No relationship:* This is seen in the normal case.

(2) *Apices lying on the roof of the canal:* In cases of this type, root formation ceases as the apices reach the roof of the canal. Some grooving is usually found on the inferior surface of the root (Fig. 7).

(3) *Apices lying to the buccal or lingual side of the canal:* This is seen when the developing roots reach the canal before their normal growth is completed. The roots are then deflected by the canal, and grooving is found on that side of the root in contact with the canal. Examination of such cases reveals that this grooving is most commonly found on the buccal side of the roots, indicating that the inferior dental canal lies lateral to the roots of the mandibular third molar (Fig. 8).

Fig. 9.

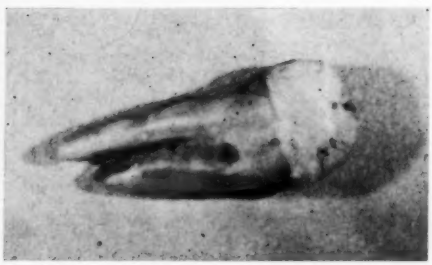

Fig. 10.

Fig. 9.—False bifurcation of the root of a lower third molar produced by the inferior dental canal.

Fig. 10.—Specimen of a horizontally impacted lower third molar, the mesial surface being grooved by the inferior dental canal.

(4) *Partial or complete encirclement of the canal by the roots:* In these cases the roots grow straight toward the canal. When they reach it, they continue developing to either side of the canal and rarely may completely encircle the canal, fusing below it. If no fusion occurs below the canal, an artificial bifurcation is produced (Fig. 9).

(5) *Other relationships:* When the mandibular third molar is lying in a horizontal position the tooth may lie on the canal, and thus part or all of the mesial surface of the root may then be related to the canal (Fig. 10).

When there is an intimate relationship between the root apices and the canal, the cortical bone which surrounds the canal may be deficient and then the periapical connective tissues of the mandibular third molar are in direct contact with the contents of the mandibular canal.

DIAGNOSIS OF RELATIONSHIP OF THE ROOTS OF THE MANDIBULAR THIRD MOLAR TO THE INFERIOR DENTAL CANAL

The figures quoted earlier in this article reveal that the relationship of the roots of an unerupted mandibular third molar to the inferior dental canal is extremely common and is possible when they are partially erupted. It is only upon radiographic evidence, however, that a reasonable diagnosis of this relationship can be made.

The true occlusal radiograph is of little use, as tooth substance lies between the film and the canal, thus obliterating the canal. Therefore, we are limited for diagnosis to the lateral radiographs, of which the intraoral radiograph is the most useful. The diagnostic features are contained in minute radiographic

Fig. 11.—Roentgenogram of lower third molar exhibiting curvature of the mesial root. Note the break in the root canal shadow and the "end-on" view of the apex of the mesial root.

definition of the canal, the periodontal outline of the roots, and the continuity of the root canals from the pulp chamber to the apical foramen. When a root shadow is superimposed on the inferior dental canal for approximately one-half the width of the latter, there may be a groove on the root apex. Where, however, the root shadow passes below that of the canal, there are two possibilities: (1) that the root lies medial or lateral to the canal and (2) that the root partially or completely encircles the canal. Further diagnostic evidence can be obtained from a study of the shadow of the root canal on the radiograph. In the case of a single-rooted mandibular third molar, if there is a break in the root canal shadow near the apex, there is a curvature of that root (Fig. 11). To ascertain whether this curvature is in a buccal or lingual direction, another film should be taken after the tube has been moved about 2 inches distal to the third molar. If the curvature is now in a forward direction, this indicates a buccal curvature; if it is in a backward direction, a

lingual curvature is indicated. In the case of two rooted mandibular third molars, both of which are crossing the canal, there is the possibility that the canal passes between these roots. If the root canal shadows join below the canal, the assumption can be made that the roots completely encircle the canal.

INJURY TO THE INFERIOR DENTAL CANAL AND ITS CONTENTS

As a result of the removal of unerupted or impacted lower third molars where roots or apices are in close proximity to the inferior dental canal, the contents of the latter are likely to be traumatized during the removal of these teeth. Observation of the symptoms of these traumatic injuries to the contents of the canal following the extraction of such teeth has suggested that these injuries may be divided into three main groups. In the first of these groups are placed those injuries caused by compression of the canal and its contents. In the second group are those injuries causing rupture of the blood vessels in the canal. The third group consists of traumatic injuries causing division of the inferior dental nerve and blood vessels.

The first group contains the most common type of injury. It is the result of a direct anatomic relationship of the root to the inferior dental canal. It will be readily appreciated that where the root partially envelops or lies in close relationship to the canal, as the tooth is moved during its extraction, compression of the canal and its contents may occur. That part of the root related to the canal may break through the walls of the canal and crush the nerve and blood vessels contained therein. The symptom of this type of injury is a paresthesia over the area of the peripheral distribution of the mental nerve on the appropriate side. It may be due to the immediate effect of a passing blow sustained by the nerve trunk from the walls of the canal which have been crushed inward by the roots during the extraction.

In the second group which includes injuries to the blood vessels of the inferior dental canal, the injuries are inflicted in a manner similar to the nerve trunk injuries already described. The damage thus produced to the blood vessels in the canal results in the occurrence of bleeding within the canal. A second method of injury is also possible. Very occasionally, foramina have been observed in that part of the root grooved by the inferior dental canal. The pulpal blood vessels here are connected to the inferior dental vessels by extremely short apical vessels which, when the tooth is extracted, may be ruptured close to the parent vessel within the canal. Hemorrhage thus occurs within the canal. Consequently, there is a slow rise of pressure in the canal, and some hours after the extraction the patient becomes aware of the onset of a paresthesia of the peripheral distribution of the nerve in question. A day or two later, traces of this hemorrhage may escape from the mental foramen, producing an ecchymosis of the overlying skin. This latter phenomenon may be absent, or it may be observed only after careful examination. In this type of injury the damage to the nerve is secondary to the damage to the blood vessels. There is a latent period before the paresthesia appears, and it is in this period that the pressure is increasing in the canal, due to

the extravasation of blood, until it reaches such a level that the resultant pressure on the inferior dental nerve interferes with the function of this sensory nerve.

In the third group the injury results in the inferior dental nerve and vessels being completely severed by the encircling roots of the third molar when it is extracted. This is a very rare occurrence, and in my experience it has been observed only twice. There results complete anesthesia of the lip and remaining teeth supplied by the nerve. Hemorrhage from the associated artery immediately following the extraction may be brisk.

The paresthesia resulting in the first two groups is of a relatively short duration. In the cases in which the nerve is completely severed, recovery or normal sensation may take up to a year, although the possibility exists that normal recovery will not take place. This is likely to happen if a length of the nerve is removed or if bone is laid down between the severed ends of the nerve before nerve regeneration has had time to take place.

Mention must be made of trauma to the canal resulting from instrumentation, especially the injudicious use of elevators. This is especially likely to occur when bone in close proximity to the canal is used as a fulcrum for an elevator. Excessive elevation force may result in a collapse of the roof of the canal, producing pressure symptoms on its contents. The inferior dental nerve and blood vessels may be divided with a bur if the latter is being used for the removal of bone in close proximity to the canal. The symptoms of these injuries are similar to those enumerated above, depending upon the degree of trauma inflicted.

When the operation is being performed under local anesthesia, an indication that the inferior dental nerve is being subjected to an undue amount of pressure is the patient's complaining of pain as the tooth is moved in a certain direction. This pain is caused by compression of the inferior dental canal and nerve, the root apex or by the root itself.

It is suggested that such symptoms as obscure neuralgic pains, neuritis, and causalgia may be a direct result of damage to the inferior dental nerve at an earlier date.

PRECAUTIONS TO MINIMIZE TRAUMA TO THE INFERIOR DENTAL CANAL

Because of the frequent relationship of the roots of unerupted and partially erupted mandibular third molars to the inferior dental canal, preoperative radiographs should be carefully studied to assess the nature of any relationship, and, bearing this in mind, the operator should plan and carry out the extraction of the tooth in such a manner as to avoid subjecting the canal to any pressure by movement of the roots or the careless use of elevators. In the case of the mesial obliquely impacted tooth, when the radiograph shows the apex to be clearly related to the roof of the canal, removal of this tooth by means of an elevator applied under the mesial surface of the crown causes the roots to rotate forward and downward, thus breaking through the walls

of the inferior dental canal and crushing the nerves and blood vessels contained within. To prevent such a complication, sufficient bone (especially distally) should be removed so that elevation allows the tooth to be immediately moved away from the canal as soon as any force is delivered by the elevator.

Where there is a lateral or lingual relation of the canal to the roots, buccolingual movements of the tooth during its extraction with forceps should be kept to a minimum, thereby reducing the trauma that may be inflicted on the canal by movement of the roots of the tooth.

If the possibility exists that the roots of the tooth completely encircle the canal, the tooth should be split vertically along its mesiodistal axis and the two halves taken out separately, thereby preventing division of the inferior dental nerve and reducing the possibility of trauma to a minimum.

When ostectomy has to be undertaken to permit the delivery of a lower third molar from its socket, sufficient bone should be removed so that the tooth can be extracted with a minimal amount of force from an elevator. Where there is marked mesial or horizontal impaction of the tooth, the canal is often found lying a very short distance below the tooth. When this bone, lying beneath the crown of the tooth and above the canal, is used as a fulcrum, undue force from the elevator may result in compression of this bone and the canal below, thus damaging the inferior dental nerve.

The removal of bone or the division of tooth substance with burs should be undertaken very carefully in the vicinity of the canal.

If the inferior dental canal is accidentally opened during the removal of a tooth or root apex, and it is suspected that tooth substance or debris has been pushed into the canal, the socket should be cleared of blood by aspiration and the fragment gently removed. Similarly, if it is known that the canal has been crushed, it should be decompressed by removing the bony spicules that have collapsed into the canal.

If the inferior dental nerve is accidentally divided, the ends should be placed in the canal so that they are as closely approximated as possible. The nerve usually unites easily, even though there may be considerable distance between the ends, so long as no obstruction lies in their path. Regeneration and recovery of sensation may take from twelve to twenty-four months. If it has not occurred at the end of this interval, it is unlikely that regeneration will occur.

SUMMARY

Attention is drawn to possible trauma to the inferior dental canal and its contents during the removal of unerupted and impacted mandibular third molars.

The position of the canal in the developing mandible is discussed, its relationships to the mandibular third molar are classified, and their diagnosis by means of radiographic examination is mentioned.

The forms of trauma that can be inflicted upon the canal and its contents, as well as the ensuing symptoms, are discussed.

Finally, precautions to minimize the risk of such injuries are briefly mentioned.

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ORAL MEDICINE

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THE ORAL TISSUES IN VITILIGO

Clifton O. Dummett, D.D.S., Tuskegee, Ala.*

INTRODUCTION

THE importance of color changes as aids in the diagnosis of diseases has been established. Normal gingival color and abnormal oral color changes have been considered.[3-6] There are still a number of systemic diseases in which there is need for information about related clinical and histopathologic changes of the oral tissues.

One of the most interesting dermatologic pathoses is vitiligo, which has been defined as an acquired, slowly progressive loss of cutaneous pigment.[1] This loss occurs in irregular, sharply defined patches which may or may not be surrounded by macroscopic hyperpigmentation. Usually there are no other significant changes in the skin which, however, does become very sensitive to light. These achromic plaques, often symmetrical, may occur in many forms and most frequently affect the hands, face, neck, and genitals.

It has been reported that the condition more often affects females.[7] That the disfigurement may become a social handicap is probably understandable.

ORAL CHANGES

The oral manifestations of vitiligo have not been described in the dental literature. A review of more than a dozen textbooks and atlases of oral pathology, oral medicine, periodontology, and oral diagnosis, as well as the *Index to Dental Literature in the English Language* did not produce any current references to this dermatologic entity.

Three case histories of persons affected with vitiligo in which the oral tissue appearances are described follow.

CASE 1.—A 37-year-old American Negro veteran of World War II, a carpenter by occupation, was hospitalized with medical diagnoses of varicose veins ruptured left leg, mixed hemorrhoids, and degenerative joint disease. The patient's face exhibited areas of

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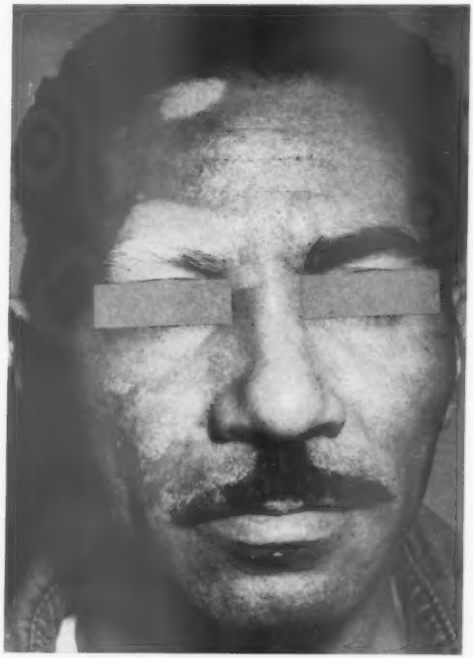

Fig. 1.—Depigmented areas in early vitiligo.

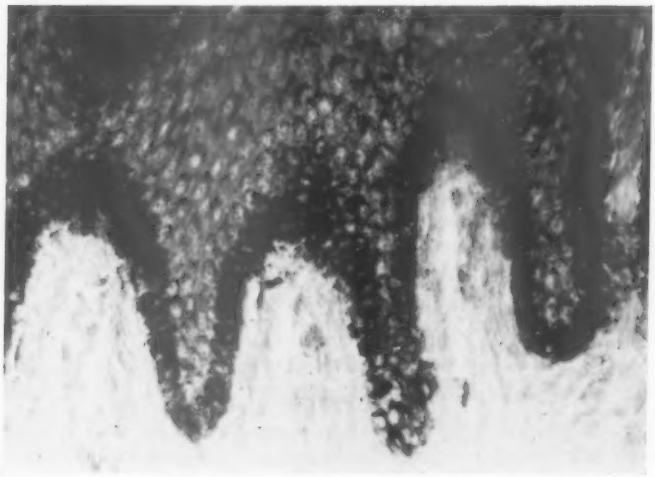

Fig. 2.—Melanoblasts in the basal layer of the gingiva.

intense depigmentation of the left eyelid and forehead (Fig. 1). He indicated that he first noted these spots seven months ago, following a scaly type of skin eruption over both tibias. The depigmented areas began as pin points, first involving the eyebrow and forehead. They spread rapidly, later affecting the right side of the face and producing a butterfly-shaped area over the cheek. The depigmentation also affected the hair, which became white in the supraorbital region and along the right angle of the mouth.

The patient's history gave no evidence of previous major illnesses. There had been no signs of depigmentation on other body areas. The patient had no symptoms of illness and was not overly concerned about the depigmentation.

The initial oral examination showed fair oral hygiene. There was periapical infection around the central incisors, which were removed on an emergency basis. A moderate amount of caries and gingival inflammation were present. The palate, tongue, lips and associated tissues were essentially normal. The gingival tissues were affected with a moderate degree of gingival pigmentation which was light brown in appearance. Histologic sections of this moderately pigmented gingiva showed the deeply staining melanoblasts in the basal layer of the epithelium (Fig. 2). At this time the intraoral tissues were not affected clinically by the depigmentation process which stopped at the external angle of the mouth.

Systemic therapy instituted by the dermatologist included exposure of the spots to erythematous doses of ultraviolet light daily, two hours after medication with 25 mg. trimethylpsoralen. This patient will be kept under observation to detect any evidence of intraoral depigmentation.

Fig. 3.—Advanced vitiligo of face with few remaining pigmented areas.

CASE 2.—A 68-year-old American Negro veteran of World War I was hospitalized with medical diagnoses of generalized arteriosclerosis, rheumatic heart disease with hypertensive cardiovascular disease, cerebral arteriosclerosis with deterioration, bronchogenic carcinoma, and vitiligo.

His physical appearance showed a generalized vitiligo involving the entire body except for flat, dark brown pigmented areas around the eyes, nose, cheeks, and mouth (Fig. 3).

The patient was alert but partially disoriented as to time and place.

The medical history of this patient revealed that oral examination in 1948 showed poor oral hygiene and areas of hyperpigmentation of the gingivae and on the tongue. Oral examination at the time of this hospitalization revealed advanced periodontal disease.

Heavy calculus formation, gingival recession, drifting, mobility, and abrasion of remaining teeth, were noted. The buccal mucosa, palate, floor of the mouth, tongue, and lips were essentially normal.

There was complete clinical depigmentation of all oral tissues (Fig. 4).

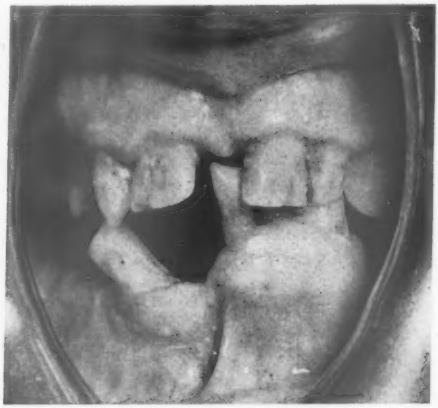

Fig. 4.—Clinical depigmentation of oral tissues in vitiliginous patient with advanced periodontal disease.

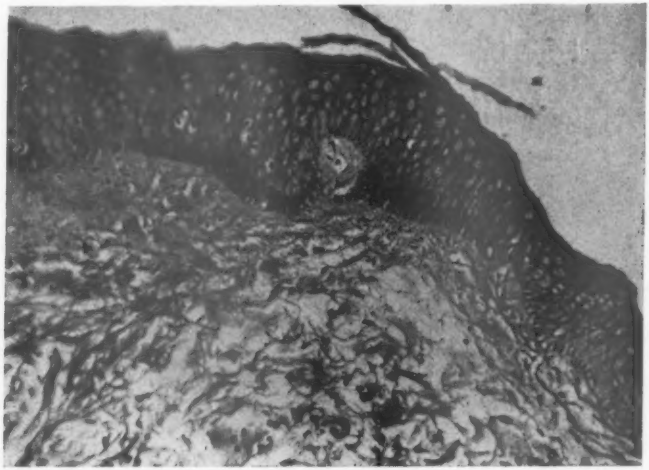

Fig. 5.—Histologic section showing loss of pigment-forming cells in clinically depigmented areas. Numerous melanoblasts may be seen in pigmented areas.

A small ovoid section of tissue (15 by 4 mm. wide and 3 mm. thick) was removed for biopsy. The tissue, taken from the neck, consisted of a plaque affected by vitiligo with a surrounding pigmented area.

Histopathologic Report (J. C. Ashhurst, M.D.): Sections of tissue showed widespread absence of pigment in the epithelium, as well as areas where the pigment was apparently being lost and other areas where it was increased (Fig. 5). Conspicuous in the upper

dermis was a wide band of basophilic degeneration of collagen as well as an increase and fragmentation of elastic fibers. The findings were consistent with vitiligo and basophilic degeneration, senile elastosis.

The diagnoses were (1) vitiligo of skin and (2) senile elastosis with basophilic degeneration of the cutis.

Fig. 6.—Two spots remain following complete facial depigmentation.

Fig. 7.—Two spots remain following complete oral depigmentation in vitiligo.

CASE 3.—An American Negro man, aged 59 years, first noticed the appearance of white spots on his body in the fall of 1934. The depigmentation was first noticed around the edges of the fingernails, the mouth, the tips of the ears, and the nose. No other signs were present. The depigmentation continued to spread over the entire body, the genitals being the last area to become depigmented. Complete depigmentation was accomplished by 1950. Extraorally, there were two dark brown spots on the left face (Fig. 6) and three spots

behind the ear and on the back of the neck. In the opinion of the patient, the spots were a little darker than his original complexion.

The patient gave a history of possessing an originally heavy gingival pigmentation. A current oral examination showed a completely edentulous mouth with pink, firm ridges. There were only two remaining purplish blue spots on the ridge of the lower left quadrant (Fig. 7). The patient has worn dentures for the past six years.

DISCUSSION

My preliminary report on the oral tissues in vitiliginous cases presents the histories of three Negro patients, two of dark brown complexion and one of light brown complexion. It has been claimed that vitiligo is found more often in Negroes than in other racial groups. There is need for further epidemiologic surveys in this area, since there has been no proof that Negroes (or any other dark-skinned peoples, for that matter) are any more susceptible to vitiligo than are Caucasians. The greater degree of conspicuousness is, of course, obvious.

Fig. 8.—Melanogingivae macula achromatica.

In so far as oral color changes are concerned, it should be noted that cases of vitiligo should be differentiated from the common picture of oral "piebald pigmentation" (Fig. 8) which has been described.[4] The latter probably should be designated as *melanogingivae macula achromatica*. Under normal conditions, histologic sections of these tissues would show the presence of varying numbers of pigment cells. Becker[2] has demonstrated microscopically the presence of some degree of pigmentation in the normal clinically nonpigmented buccal mucosa and has concluded that pigmentation of the buccal mucosa appeared to be normal.

CONCLUSION

Studies of the oral phases of vitiligo should accompany research on dermatologic and systemic aspects. The absence or decrease of oral pigmentation is

as important a factor as the presence or increase of melanin. Information about these matters will constitute a major contribution to the increasingly important and rapidly expanding science of oral diagnosis.

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PHARMACOLOGY AND THERAPEUTICS

A NEW VEHICLE (ORABASE) FOR THE APPLICATION OF DRUGS TO THE ORAL MUCOUS MEMBRANES

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With the Assistance of Ferdinand Tuoti, D.M.D., John D. Piro, D.D.S., Jack Budowsky, D.D.S., Robert Herlands, D.D.S., Robin M. Rankow, D.D.S., M.D., and Herbert F. Silvers, D.D.S.

ATTEMPTS at the treatment of chronic lesions of the oral mucous membranes, such as the keratoses, desquamative stomatitis (or gingivosis), recurrent ulcerative stomatitis, pemphigus, erythema multiforme, drug eruptions, etc., have always been hampered to the point of relative ineffectiveness by the difficulty in maintaining medications at the site of application. In addition to the lack of effectiveness of the medication per se, this failure was due, in part, to the inability of the vehicle in which the medication was incorporated to adhere to the site where it was applied.

The properties of a vehicle have long been appreciated as being of the utmost importance in dermatology. No such parallel interest has been seen in oral therapeutics, where the practitioner cannot even avail himself of the mechanically protective properties of the coverings used in dermatologic practice because of the uncontrollable factors of salivation, tongue movement, deglutition, etc.

From the School of Dental and Oral Surgery, Columbia University; the Institute of Cancer Research, College of Physicians and Surgeons, Columbia University; and the School of Public Health and Administrative Medicine of the Faculty of Medicine, Columbia University.

The adhesive vehicle used in this study is available from E. R. Squibb & Sons as Orabase and was supplied by The Squibb Institute for Medical Research, New Brunswick, New Jersey. It contains gelatin, pectin, carboxymethyl cellulose, and Plastibase.

Portions of this study were carried out by members of the William Jarvie Society for Dental Research (School of Dental and Oral Surgery, Columbia University), whose cooperation is gratefully acknowledged herewith: F. Berlin, A. Dell, M. W. Diamond, A. E. DiCerbo, R. Dubner, M. K. Gellis, W. A. Gutstein, E. Herzig, D. E. Hopp, N. Kahn, E. Katz, I. J. Leiling, K. D. Levin, R. Lifschutz, M. G. Mage, S. Merl, M. P. Merritt, S. M. Murphy, N. R. Napoli, S. S. Osleeb, A. C. Palermo, M. C. Rennert, J. Rosen, M. Ross, R. Rothman, L. I. Slawin, C. S. Solomon, T. Spier, S. M. Steinerman, and G. H. Stoller.

Vehicles previously used in coating the oral mucous membranes have included tincture of benzoin, petrolatum, Carbowax, various oils, and others. None of these vehicles has proved satisfactory. Rothner and associates[1] reported that carboxymethyl cellulose in petrolatum represented an improved vehicle for the incorporation of penicillin. There has been no further report of the use of this substance as a vehicle for other oral medications. Thus, a suitable vehicle for the application of drugs to the oral mucous membranes is needed.

This report describes a new vehicle, compounded of four essentially nontoxic ingredients, which has the ability to adhere and maintain itself at the site of application over relatively prolonged periods, thereby (1) increasing the potential effectiveness of medications by maintaining higher concentrations of the agent at the site of a given lesion; (2) decreasing the total amount of material which need be applied; (3) increasing the duration over which the material

Table I. Recordings on Twenty-One Subjects Following the Application of Approximately 60 mg. of Adhesive Vehicle to Various Sites

Patient	Dorsum of Tongue	Hard Palate	Lower Lingual Anterior Gingivae	Mucosa of Cheek
1	15			
2		40	30	40
3	66	15	25	35
4		20	32	10
5	25	20	33	42
6		30	30	25
7	63	40	40	10
8	33	23	25	25
9	17	10	11	12
10		25	18	29
11	19	14	14	19
	28			19
12	11	20	10	15
13	18	26	24	20
14		15	17	15
15		37	30	37
16		13	14	18
17	10			
18	15			
19	25			
20	31			
21	29			54
Number of applications	15	15	15	17
Range (minutes)	10-66	10-40	10-40	10-54
Average duration at site (minutes)	25	23	24	25

will remain in situ; (4) decreasing the amount of material which, following displacement from the area, would be swallowed and might therefore be available for undesired systemic activity; and (5) providing a useful mechanical protective coating over the lesion.

This report will describe the results of investigations designed to study those properties of this new adhesive material (especially duration of maintenance at a site of application) which suggest its usefulness as a vehicle in which to incorporate various therapeutic agents for application to the oral mucous membranes.

This article is concerned, therefore, chiefly with "time studies" designed to ascertain the duration of effective action which can be expected with the new vehicle when it is applied to various sites of the oral mucous membranes as studied by various techniques.

METHODS

The subjects of this study were divided into four groups. Group I was composed of twenty-one male subjects, aged 22 to 26, members of the William Jarvie Society for Dental Research of the School of Dental and Oral Surgery of the Faculty of Medicine, Columbia University. Approximately 60 mg. of the experimental adhesive material was applied to various oral mucous membrane sites, and the time of complete dissolution or disappearance of the adhesive during the course of normal function other than eating was recorded by each subject. Disappearance was determined by the loss of subjective evidence, awareness, or consciousness of its presence in the area. Presence or absence was also ascertained by various movements of the mucous membranes and by sensory contact with these areas by the tongue. The sites of application and the findings of this study are shown in Table I.

Group II was composed of thirty patients, aged 12 to 70, four male and twenty-six female, all of whom were under treatment for various chronic lesions of the oral mucous membranes. These patients applied approximately 250 mg. of the adhesive vehicle to various areas of the mouth and recorded the period of time during which the adhesive material remained at the site of application. The adhesive material either had a therapeutic agent incorporated in it or was used by itself as a placebo. Application of the medication was performed by the patient on four to six occasions during the day for at least one day but usually several days. The sites of application for these subjects and the findings are summarized in Table II.

Group III was composed of twenty men, aged 22 to 30, volunteer subjects or patients who presented for treatment in the Department of Periodontology of the School of Dental and Oral Surgery. These patients were studied during normal function other than eating following the application of 250 mg. of the vehicle to various areas of the gingivae, following which the duration of maintenance at the site of application was observed visually by one of the investigators. The sites of application and the findings are shown in Table III.

Group IV was composed of forty-eight male subjects, aged 45 to 75, all inpatients of the Francis Delafield Hospital. Approximately 125 mg. of the vehicle was applied to various areas of the oral mucous membranes of these subjects during the course of normal function other than eating. The patients were observed visually for the presence or absence of the medication in the area of application at various specific time intervals. The number of application sites and the duration of adherence of the vehicle in these patients are shown in Table IV.

TABLE II. RECORDINGS ON THIRTY SUBJECTS FOLLOWING THE APPLICATION OF APPROXIMATELY 250 MG. OF ADHESIVE VEHICLE TO VARIOUS SITES

		AVERAGE REPORTED TIMES BY AREA IN MINUTES						
PATIENT	NUMBER OF APPLICATIONS	DORSUM OF TONGUE	HARD PALATE	ANTERIOR LABIAL GINGIVAE	LOWER LINGUAL ANTERIOR GINGIVAE	MUCOSA OF CHEEK	INNER SURFACE OF LOWER LIP	MUCOBUCCAL FOLD
1	30	30						
2	27	86						
3	1						90	
4	26					81		
5	11						63	
	12				46			
	12					104		
6	4						130	
	6				49			
	5		100					
7	11				67			
	11	63						
	11		75					
8	8						90	
	8	63						
	8		67					
9	7					32		
	4				56			
	5	27						
10	19						48	
11	7						120	
	7	46						
12	13					255		
13	6						55	
	6	70						
14	9	47						
15	5				210			
16	15			247				
17	11	103						
18	16			131				
19	10			57				
	10							57
20	16	44						
21	13					88		
22	10			115				
23	8					31		
	7						147	
24	8			94				
25	17						105	
	17						185	
26	15							248
27	7			14				
28	16					45		
29	12					41		
30	10					140		
Number of patients		10	3	6	5	9	10	2
Number of applications	497	130	24	66	38	117	97	25
Range (minutes)		27-103	67-100	14-247	46-210	31-255	55-185	57-248
Average duration at site (minutes)		58	81	109	85	91	103	152

RESULTS

The results of this study are included in Tables I through IV and are summarized in Table V. Observations covered a total of 784 applications in 119 patients, including fifty-nine subjects to whom the vehicle was applied on one to three occasions, thirty-three subjects to whom the vehicle was applied on four to eight occasions, fourteen subjects to whom the vehicle was applied on nine to fifteen occasions, seven subjects to whom the vehicle was applied on sixteen to twenty-five occasions, and six subjects to whom the vehicle was applied on twenty-six or more occasions.

TABLE III. RECORDINGS ON TWENTY SUBJECTS FOLLOWING THE APPLICATION OF APPROXIMATELY 250 MG. OF ADHESIVE VEHICLE TO VARIOUS SITES

PATIENT	ANTERIOR LABIAL GINGIVAE	MUCOBUCCAL FOLD	LOWER LINGUAL ANTERIOR GINGIVAE
1	20		
	15		
2	30		
3	20		
	15		
4	30		
5	30		
6	103	182	
7	105	155	
8		35	62
9		75	65
10	97	97	
11	105		
12	197		
13	160		
14	172		
15	311		
16	70		
17	255		
18	40		
19	60		
20	43		
Number of patients	20	5	2
Number of applications	20	5	2
Range (minutes)	15-311	35-182	62-65
Average duration at site (minutes)	94	108	64

Variations were observed in the duration of maintenance at the site, depending upon site of application and approximate amount of vehicle used.

The average duration of maintenance (and range) for each area and dosage level studied (Groups I to IV) is summarized in Table V. The average duration of maintenance for each of the anatomic sites studied was as follows: dorsum of the tongue—twenty-five minutes for Group I, fifty-eight minutes for Group II, and fifteen minutes for Group IV; the hard palate—twenty-three minutes for Group I, eighty-one minutes for Group II, and thirty-three minutes for Group IV; anterior labial gingivae—twenty-four minutes for Group I, 109 minutes for Group II, ninety-four minutes for Group III, and fifty-six minutes for Group IV; lower lingual anterior gingivae—eighty-five minutes for Group

TABLE IV. RECORDINGS ON FORTY-EIGHT SUBJECTS FOLLOWING THE APPLICATION OF APPROXIMATELY 125 MG. OF ADHESIVE VEHICLE TO VARIOUS SITES

PATIENT	DORSUM OF TONGUE	HARD PALATE	ANTERIOR LABIAL GINGIVAE	LOWER LINGUAL ANTERIOR GINGIVAE	MUCOSA OF CHEEK
1	0*		60		0*
			60		
2	30		30		30
			30		
3	0*		0*		0*
			30		
4			60		30
			60		
5	0*		90†		0*
			60		
6	0*		0*		0*
			0*		
7	0*		30		0*
			90†		
8	0*		60		0*
			30		
9	0*		60		30
			90†		
10	0*		60		60
			60		
11		10		30†	30†
12		10		10	10
13		30†		30†	30†
14		20		30†	30†
15		30†		30†	30†
16		30†		30†	30†
17		30†		30†	30†
18		30†		30†	30†
19		30	30	30	30
20	15	60	75	30	15
			75†		
21	30	30	75	30	30
			75†		
22	75†	75†	75†	75	75†
			75†		
23	15	30	75†	75	30
			15		
24	30	75†	75†	30	75
			45		
25	30	75†	30	30	75†
			75†		
26		15	60†	45	45
			60†	60†	45
			60†		
27		15	60†	45	60†
		45	60†	15	60†
			60†		
			60†		
28		30	60†	45	60†
		15	60†	30	15
			60†		
			60†		
29		0	60	0*	0*
		0	60	0*	45
			30		
			15		
30		60†	60†	60†	60†
		60†	60†	60†	60†
			60†		
			60†		
31		15	45	15	15
		15	60†	15	45
			60†		
			60†		

(Continued on following page.)

TABLE IV—CONT'D

PATIENT	DORSUM OF TONGUE	HARD PALATE	ANTERIOR LABIAL GINGIVAE	LOWER LINGUAL ANTERIOR GINGIVAE	MUCOSA OF CHEEK
32			60†		
			60†		
33			60†		
			60†		
34			60†		
			60†		
35			50†		
			50†		
36			50†		
			50†		
37			55†		
			55†		
38			60†		
			60†		
39			60†		
			60†		
40			60†		
			60†		
41			60†		
			60†		
42			60†		
			60†		
43			60†		
			60†		
44			60†		
			60†		
45			60†		
			60†		
46			50†		
			50†		
47			60†		
			60†		
48			60†		
			60†		
Number of patients	16	21	40	21	31
Number of applications	16	27	91	27	37
Range (minutes)	0*-75	0*-75	0*-90	0*-75	0*-75
Average duration at site (minutes)	15	33	56	34	45

*In this group, a check of patients for evidence of the presence of the vehicle at the site of application was made usually at approximately thirty-minute intervals. A zero reading indicates that the vehicle could not be observed after the first time check at thirty minutes. A recording of the last time check at which the vehicle was seen (0 minutes) was thus made.

†Indicates termination of period during which subject could be studied. Vehicle was still in place. Recording is thus a minimal one.

II, sixty-four minutes for Group III, and thirty-four minutes for Group IV; mucosa of the cheek—twenty-five minutes for Group I, ninety-one minutes for Group II, and forty-five minutes for Group IV; inner surface of the lower lip—103 minutes for Group II; mucobuccal fold—152 minutes for Group II and 108 minutes for Group III.

The minimum period of maintenance was observed on the dorsum of the tongue in Group IV, in which area an average duration of fifteen minutes (range 0* to 75 minutes) was observed following the application of 125 mg. of

*In this group, a check of patients for evidence of the presence of the vehicle at the site of application was made usually at approximately thirty-minute intervals. A zero reading indicates that the vehicle could not be observed during the first time check at thirty minutes. A recording of the last time check at which the vehicle was seen (0 minutes) was thus made in order to take the most conservative estimate.

TABLE V. SUMMARY OF DATA FOR RECORDED DURATION OF MAINTENANCE OF VEHICLE FOR VARIOUS SITES AND DOSAGES

	NUMBER OF PATIENTS					NUMBER OF APPLICATIONS					DURATION AT SITE (MINUTES)				
												AVERAGE			
	GROUP I	GROUP II	GROUP III	GROUP IV	TOTAL	GROUP I	GROUP II	GROUP III	GROUP IV	TOTAL	RANGE	GROUP I	GROUP II	GROUP III	GROUP IV
Dosage (mg.)	60	250	250	125	--	60	250	250	125	---		60	250	250	125
Dorsum of tongue	15	10		16	41	15	130		16	161	0*-103	25	58		15
Hard palate	15	3		21	39	15	24		27	66	0*-100	23	81		33
Anterior labial gingivae	15	6	20	40	81	15	66	20	91	192	0*-311	24	109	94	56
Lower lingual anterior gingivae		5	2	21	28		38	2	27	67	0*-210		85	64	34
Mucosa of cheek	17	9		31	57	17	117		37	171	0*-255	25	91		45
Inner surface of lower lip		10			10		97			97	55-185		103		
Mucobuccal fold		2	5		7		25	5		30	35-248		152	108	

*In this group, a check of patients for evidence of the presence of the vehicle at the site of application was made usually at approximately thirty-minute intervals. A zero reading indicates that the vehicle could not be observed during the first time check at thirty minutes. A recording of the last time check at which the vehicle was seen (0 minutes) was thus made.

vehicle. The maximum period of maintenance was observed in the mucobuccal fold area in Group II, in which area an average duration of 152 minutes (range 57 to 248 minutes) was observed following the application of approximately 250 mg. of vehicle.

The average durations noted above are, in general, in agreement with the distribution which might be expected on the basis of the activity of the various sites, the resultant expectancy of mechanical dislodgment of vehicle and its availability for removal by salivary currents, and the amounts of vehicle applied.

In all instances, the recording of the duration of maintenance of the vehicle was that time check at which the material was last observed or "felt" rather than a midpoint (or other arbitrary point) between the time at which the material was last seen and the time check at which it was found to have disappeared. Thus, in all instances the duration-of-maintenance figures reported herewith are minimum times.

No evidences of irritation, side reaction, or toxicity were observed, either locally or systemically, following single or repeated applications of the adhesive vehicle. One person, suffering from desquamative gingivitis, attempted repeatedly to remove all traces of the vehicle from the mucous membranes (for cosmetic reasons) and thereby removed the delicate and imperfect epithelial covering from an already sensitive and inflamed mucosa. No other deleterious action was noted in any patient, including those with sensitive, ulcerated, or inflamed lesions for which they were under treatment. A number of patients complained about the gummy character of the vehicle; all but one, however, were satisfied to continue using the vehicle preparation when its useful attributes were clarified to them.

It appears that oral tissues accept this vehicle adhesive quite well. Repeated application of the unmedicated vehicle did not cause any macroscopic changes in the oral mucous membranes. In addition to the results cited here, this adhesive vehicle has been used as a denture adhesive in 100 patients for periods of time ranging from one day to four weeks without evidence of tissue irritation.

Since all materials placed in the mouth eventually are swallowed, any systemic activity which a vehicle may possess must be considered. The components of this vehicle (Plastibase, carboxymethyl cellulose, pectin, and gelatin) have all been found relatively free of deleterious, toxic, or allergenic properties when swallowed in reasonable amounts.

SUMMARY

A new vehicle for the application of therapeutic agents to the oral mucous membranes is described. Various clinical tests were undertaken on a total of 119 patients (784 applications) in order to study the usefulness of this material as a vehicle for the prolonged application of medications to the oral mucous membranes.

The findings indicate that when approximately 60 mg. (Group I), 250 mg. (Groups II and III), and 125 mg. (Group IV) of this vehicle adhesive are applied to various sites of the oral cavity, the average duration of maintenance

was as follows: dorsum of the tongue—twenty-five, fifty-eight, and fifteen minutes for Groups I, II, and IV, respectively; hard palate—twenty-three, eighty-one, and thirty-three minutes for Groups I, II, and IV, respectively; anterior labial gingivae—twenty-four, 109, ninety-four, and fifty-six minutes for Groups I, II, and III, and IV; lower lingual anterior—eighty-five, sixty-four, and thirty-four minutes for Groups II, III, and IV; mucosa of the cheek—twenty-five, ninety-one, and forty-five minutes for Groups I, II, and IV; inner surface of the lower lip—103 minutes for Group II; and mucobuccal fold—152, and 108 minutes for Groups II and III, respectively.

In no instance was there observed any evidence of irritation or other side reaction or toxicity, either local or systemic, due to the vehicle being studied.

These data indicate a potential usefulness of this material as a vehicle for topical oral medications and mechanical protection in the oral cavity.

The authors are indebted to Mrs. Florence Moore, Miss Doris Tormez, Miss Joan Graham, Miss Ida Perez, Mrs. Eileen Geller, Mrs. Helene W. Kutscher, Miss Evelyn Wirth, Mrs. Eleanor Weischadle, and Miss Rudell Osgood for their appreciated assistance.

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ORAL ROENTGENOLOGY

American Academy of Oral Roentgenology

Arthur H. Wuehrmann, Editor

ROENTGENO-QUESTIONS

I AM *considering the purchase of a new x-ray unit. Should I buy a 70 or 90 KVP unit?*

X-ray units with a peak kilovoltage of 90 are seldom used at 90 for all exposures. More common is the use of exposures with the kilovoltage adjusted for the various dental regions to be exposed, according to the thickness and density of the region. A fixed exposure time is used with the variable voltage factor, so that each film has the same density. This also allows the operator to use the "reset" features of the timers to advantage. Higher kilovoltage for the thicker regions, such as the upper molar region, and lower kilovoltages for the thinner, less dense regions, such as the anterior of the mandible, are commonly used. Thus, the kilovoltage, the factor which influences the penetration of the radiation, is adjusted to suit the thickness of the region to be studied. The higher the kilovoltage, the greater the penetration and the less the absorption in the tissues overlying the dental structures. This results in less unnecessary radiation to the patient and in shorter exposure times. The films exposed to kilovoltages ranging up to 90 will exhibit longer-scale contrast, as compared to those exposed to kilovoltages in the lower ranges, such as 40 to 65. Long-scale contrast films exhibit more detail and greater tissue differentiation. If you will keep in mind the points mentioned—shorter exposure times, less radiation administered to the patient, and the long-scale contrast qualities of the film when higher kilovoltages are used—you can then decide if these factors are helpful and desirable to you and purchase an x-ray unit of the type you wish.

The American Academy of Oral Roentgenology solicits from the readers of ORAL SURGERY, ORAL MEDICINE AND ORAL PATHOLOGY any questions which deal with technical or interpretive aspects of oral roentgenology. These questions should be sent directly to the editor of this section, Dr. Arthur H. Wuehrmann, School of Dentistry, University of Alabama Medical Center, Birmingham, Alabama; the editor will distribute them for reply to a suitable group within the Academy. Questions, with the answers, will be published at as early a date as possible in "Roentgeno-questions." Questions, especially those of an interpretive nature, should ordinarily be accompanied by good-quality roentgenograms and a pertinent history. The names of the questioner and the respondent will not be published.

RELATIVE FILM SPEEDS OF COMMONLY USED INTRAORAL FILM

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INTRODUCTION

AT THE present time manufacturers of dental x-ray film do not code the speeds of their various films in such a manner that they can be readily compared with the speeds of other films of the same manufacturer or various films of competitive manufacturers. Cognizance of the need for using the fastest practical film in dental roentgenography in order to reduce the hazards of radiation has necessitated a study of the comparative speeds of films used in the dental office. This article will report the method and the findings of such a study.

METHOD

Sample periapical films of various speeds and the occlusal film of one manufacturer were obtained through the cooperation of the film manufacturers. All films having the same descriptive titles were of the same emulsion

TABLE I

FILM TYPE	X-RAY MACHINE				CONTROL FILM	AVERAGE —LESS FOG CONTROL FILM
	G. E. 90	WEBER-90 12-R	RITTER DUAL-X	XRM 90P		
Kodak						
Ultra-Speed DF-58	2.25	1.55	2.55	1.75	0.11	1.92
Radia-Tized DF-7	0.57	0.36	0.59	0.41	0.1	0.38
Occlusal DF-45	1.80	1.25	2.05	1.40	0.13	1.50
Du Pont						
Lightning Fast (LF-1)	3.0	2.15	3.05	2.5	0.23	2.45
Intermediate D-1	0.46	0.32	0.58	0.37	0.1	0.33
Slow Speed S-1	0.3	0.19	0.32	0.22	0.08	0.18
Minimax						
Extra Fast EFS	1.25	0.74	1.30	0.95	0.13	0.93
Intermediate BS	0.46	0.3	0.52	0.37	0.16	0.25
Rinn						
Extra Fast EF-1	1.5	0.95	1.75	1.15	0.19	1.15
Intermediate DC-1	0.41	0.32	0.45	0.35	0.16	0.22

Light transmission densities were obtained under the following conditions: By means of an open-end plastic cone, the films were exposed by suspension in air. *Exposure factors:* 65 KVP, 10 Ma., 1 second, 24 inch target-to-film distance, no added filtration.

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number. Exposures were made of the different films, with four different x-ray machines used under each of four different exposure conditions; thus, each type of film was exposed sixteen different ways. The four exposure conditions that were used are clearly stated in the footnotes below Tables I, II, III,

TABLE II

FILM TYPE	X-RAY MACHINE				CONTROL FILM	AVERAGE —LESS FOG CONTROL FILM
	G. E. 90	WEBER-90 12-R	RITTER DUAL-X	XRM 90P		
Kodak						
Ultra-Speed DF-58	1.92	1.17	1.66	1.35	0.13	1.40
Radia-Tized DF-7	0.31	0.46	0.4	0.35	0.09	0.29
Occlusal DF-45	1.6	1.1	1.45	1.2	0.15	1.19
Du Pont						
Lightning Fast (LF-1)	2.6	1.72	2.5	1.95	0.24	1.95
Intermediate D-1	0.38	0.27	0.33	0.31	0.11	0.21
Slow Speed S-1	0.26	0.19	0.23	0.22	0.11	0.12
Minimax						
Extra Fast EFS	1.1	0.67	0.87	0.76	0.15	0.70
Intermediate BS	0.41	0.3	0.36	0.35	0.17	0.19
Rinn						
Extra Fast EF-1	1.25	0.8	0.31	0.92	0.18	0.64
Intermediate DC-1	0.36	0.28	0.34	0.3	0.15	0.17

Light transmission densities were obtained under the following conditions: By means of an open-end plastic cone, the films were exposed by suspension in air. *Exposure factors:* 65 KVP, 10 Ma., 1¼ seconds, 24 inch target-to-film distance, 1 mm. aluminum added filtration.

TABLE III

FILM TYPE	X-RAY MACHINE				CONTROL FILM	AVERAGE —LESS FOG CONTROL FILM
	G. E. 90	WEBER-90 12-R	RITTER DUAL-X	XRM 90P		
Kodak						
Ultra-Speed DF-58	3.4	2.1	3.5	2.0	0.15	2.6
Radia-Tized DF-7	0.9	0.55	1.2	0.45	0.1	0.77
Occlusal DF-45	2.0	1.6	2.5	1.3	0.15	1.7
Du Pont						
Lightning Fast (LF-1)	3.5	2.7	3.5	2.1	0.24	2.7
Intermediate D-1	0.76	0.52	1.0	0.41	0.1	0.57
Slow Speed S-1	0.48	0.3	0.52	0.26	0.09	0.3
Minimax						
Extra Fast EFS	2.35	1.4	2.7	1.1	0.15	1.73
Intermediate BS	0.67	0.49	0.9	0.42	0.14	0.48
Rinn						
Extra Fast EF-1	2.35	1.6	3.0	1.25	0.19	1.86
Intermediate DC-1	0.65	0.47	0.35	0.36	0.15	0.3

Light transmission densities were obtained under the following conditions: By means of an open-end plastic cone, the films were exposed by simulating in vivo conditions through the use of a waxed skull (the wax is of a molecular structure that compares favorably with soft tissue). The portion of the film scanned for density was that covered by wax simulating the buccal tissues (noncalcified structures). *Exposure factors:* 65 KVP, 10 Ma., 1¾ seconds, 20 inch target-to-film distance, no added filtration.

and IV. All films exposed under the same exposure conditions, together with a nonexposed film of each type as a control for pre-exposure emulsion fog, were processed in total darkness under standard darkroom conditions as

recommended by the manufacturers. The density of each film exposed was recorded with a Weston densitometer (No. 877, type 6). An average of the results was obtained for each film type exposed under the same conditions. From this average was subtracted the density of the fog control film. Tables I, II, III, and IV show the results for each film type under varying conditions

TABLE IV

FILM TYPE	X-RAY MACHINE				CONTROL FILM	AVERAGE —LESS FOG CONTROL FILM
	G. E. 90	WEBER-90 12-R	RITTER DUAL-X	XRM 90P		
Kodak						
Ultra-Speed DF-58	2.9	1.75	2.55	2.06	0.15	2.17
Radia-Tized DF-7	0.79	0.44	0.61	0.5	0.1	0.49
Occlusal DF-45	1.92	1.3	1.8	1.55	0.15	1.49
Du Pont						
Lightning Fast (LF-1)	2.8	1.85	2.5	2.3	0.24	2.12
Intermediate D-1	0.65	0.36	0.5	0.42	0.1	0.38
Slow Speed S-1	0.37	0.23	0.33	0.26	0.1	0.2
Minimax						
Extra Fast EFS	1.8	1.05	1.5	1.25	0.16	1.24
Intermediate BS	0.6	0.4	0.5	0.49	0.16	0.34
Rinn						
Extra Fast EF-1	2.3	1.15	1.7	1.4	0.19	1.45
Intermediate DC-1	0.54	0.35	0.45	0.41	0.15	0.29

Light transmission densities were obtained under the following conditions: By means of an open-end plastic cone, the films were exposed by simulating in vivo conditions through the use of a waxed skull (the wax is of a molecular structure that compares favorably with soft tissue). The portion of the film scanned for density was that covered by wax simulating the buccal tissues (noncalcified structures). *Exposure factors:* 65 KVP, 10 Ma., 1¾ seconds 20 inch target-to-film distance, 1 mm. aluminum added filtration.

TABLE V. A COMPOSITE OF AVERAGE FILM DENSITIES AS OBTAINED FROM TABLES I TO IV

FILM TYPE	TABLE I	TABLE II	TABLE III	TABLE IV	AVERAGE
Kodak					
Ultra-Speed DF-58	1.92	1.40	2.6	2.17	2.02
Radia-Tized DF-7	0.38	0.29	0.77	0.49	0.48
Occlusal DF-45	1.50	1.19	1.7	1.49	1.47
Du Pont					
Lightning Fast (LF-1)	2.45	1.95	2.7	2.12	2.31
Intermediate D-1	0.33	0.21	0.57	0.38	0.37
Slow Speed S-1	0.18	0.12	0.3	0.2	0.20
Minimax					
Extra Fast EFS	0.93	0.70	1.73	1.24	1.15
Intermediate BS	0.25	0.19	0.48	0.34	0.32
Rinn					
Extra Fast EF-1	1.15	0.64	1.86	1.45	1.28
Intermediate DC-1	0.22	0.17	0.3	0.29	0.25

of exposure. As a final step, the average densities, less fog, for each film type taken under varying conditions of exposure were averaged, and these results were arranged for purposes of determining the relative film speeds. Table V shows the averaging of the film densities obtained under the four different exposure techniques; Table VI arrays the films according to density

and restates these densities in terms of multiples of the least dense film. These multiples can be considered as the average relative film speeds. Thus, under constant conditions, to obtain the same density, a film having a relative film speed of 1 would have to be exposed approximately twice as long as a film having a film speed of 1.9; and an emulsion having a film speed of 11.6 would have to be exposed only one-seventh as long as a film having a film speed of 1.6.

TABLE VI. RELATIVE FILM SPEEDS OF FILMS EXAMINED

ARRAYED AVERAGES	FILM	MULTIPLES OF LEAST DENSE FILM* OR RELATIVE FILM SPEEDS
0.20	Du Pont S-1	1.0
0.25	Rinn DC-1	1.3
0.32	Minimax BS	1.6
0.37	Du Pont D-1	1.9
0.48	Kodak DF-7	2.4
1.15	Minimax EFS	5.8
1.28	Rinn EF-1	6.4
1.47	Kodak DF-45	7.4
2.02	Kodak DF-58	10.1
2.31	Du Pont LF-1	11.6

*Multiples of the least dense film indicate the relative film speeds of those films examined under various conditions.

CONCLUSION

This clinical study demonstrates the relative film speeds of the commonly used dental periapical films and the occlusal type of film of one manufacturer. These results were obtained by using several different x-ray machines under varying exposure techniques. The findings will permit the practitioner to evaluate the extent to which he is using film speed in reducing the radiation hazard to his patient. The use of fast film, more than any other factor, will considerably reduce the patient's exposure to x-radiation during the making of dental roentgenograms.

ORAL PATHOLOGY

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METASTATIC CARCINOMA OF THE JAWS SECONDARY TO PRIMARY CARCINOMA OF THE BREAST

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THE majority of carcinomas of the mouth are primary in orgin. Occasionally, however, secondary osseous deposits occur in the jaws.

The number of reported cases of tumor metastases to the jaws from distant primary sites, however, appears to be small despite the fact that primary tumors of such organs as the breast, thyroid, prostate, ovary, and lungs commonly metastasize to bone. Stern and Shepherd[1] cited fifty-five cases of metastatic carcinoma of the jaws reported in the literature.

There appears to be some difference of opinion among authors as to which primary sites are most responsible for secondary osseous deposits. Abrams and colleagues,[2] in a study to determine the incidence of osseous metastases, found that these were most common in carcinoma of the breast, where 73 per cent spread to bone. Sharp and associates,[3] however, cited primary tumors in the prostate as most commonly metastasizing to bone. Willis[4] supports Abrams and co-workers in rating primary tumors of the breast as most commonly metastasizing to bone. Meyer,[5] however, found that by far the greatest number of osseous secondary lesions in a series of 320 cases diagnosed at necropsy were derived from bronchial primary sites. Geschickter and Copeland[6] state that their impression is that in the late stages of disease, extension to bone occurs in nearly 50 per cent of the cases of breast, renal, prostatic, and bronchial carcinoma and is clinically manifest in about 25 per cent of the cases before the termination of the disease.

Again there is some difference of opinion as to which primary site is most responsible for secondary deposits in the jaws. Stern and Shepherd[1] report that from a study of published cases of metastatic carcinoma to the jaws the primary site was most frequently the thyroid gland. Moorman and Shafer[7] found the most common primary site of mandibular metastases to be the breast. Sharp and associates[3] also found the breast to be the most frequent primary site metastasizing to the jaws.

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In view of the high incidence of osseous metastases from carcinoma of the breast, few cases of secondary deposits in the jaws have been reported. In an analysis of bone metastases in 100 cases of carcinoma of the breast, Geschickter and Copeland do not make any specific mention of metastases being found in the jaws. The spine, pelvis, and femur are mentioned as being the most common sites of secondary deposits. The cranial bones accounted for 13 per cent of the total. This survey suggests that metastases to the jaws from primary carcinoma of the breast are uncommon. Blackwood[8] reported a case of secondary carcinoma of the mandibular condyle secondary to carcinoma of the breast and reports that only twenty-two other cases have been published in which metastases from breast carcinoma had been found in the jaws. A further case has recently been reported by Cohen.[9]

It is generally thought that the incidence of carcinoma is increasing; therefore, these rare occurrences of secondary deposits in the mandible are likely to be seen more often. Though few cases of metastatic carcinoma of the jaws have been reported, Cohen[9] suggests that they are more common than is suspected. A clinical diagnosis may be missed, or they are symptomless; an examination of the jawbones is not a part of routine autopsy technique. As Cohen points out, an indication that metastases to the mandible are missed is supplied by the findings of Moorman and Shafer,[7] who examined ten carcinoma patients (breast, thyroid, prostate, and kidney primary tumors), none of whom had complained of oral symptoms. Of these, three were found to have secondary deposits in the mandible.

There is, however, an anatomic factor that may play a part in determining the incidence of metastases occurring in the jaws. The formation of a secondary tumor in bone is dependent upon the presence of red marrow where thin-walled channels offer a suitable site for the lodgment and proliferation of the tumor emboli. In the mandible therefore, secondary deposits should be most commonly found in the molar region. The infrequency of metastases to the mandible may possibly be due to the absence of bone marrow in the mandible, especially in patients in the age groups where carcinoma is most commonly found. This view was substantiated by Box[10] who examined a series of mandibles and found that only 25 per cent contained red marrow, which occurred in small discrete patches.

One of the first authors to discuss the method of spread of primary tumors to bone was von Recklinghausen. He proposed the theory that they spread into the bone marrow via the blood stream. He based this theory on three factors: first, that metastases in bone occurred within the medullary cavity and reached the periosteum only by extension from the interior; second, when the subperiosteal tissue was invaded it was always in the region of the large foramina which served as a point of egress for the veins; and third carcinoma cells in marrow lay in definite channels which were arranged in a manner similar to that of the veins present in the marrow.

This theory of a hematogenous spread was supported by Paget,[12] Schmidt,[13] and Piney.[14]

Batson[15] confirmed this theory. He demonstrated that the vertebral veins were a valveless plexus which formed a separate system or pool for blood which had been forced out of the thoraco-abdominal cavity by an act such as coughing. He showed that material injected into the breast venules entered this vertebral system via the intercostal veins and "duplicated the pattern of aberrant breast cancer spread" into the spine, ribs, skull, etc. The autopsy findings in studies of metastasis in breast carcinoma by Warren and Witham[18] stress the importance of dissemination via the blood vessels.

Handley,[16] however, suggested that breast cancer was disseminated to bone by lymphatic permeation via the deep fascial lymphatics. This theory was supported by Carnett and Howell.[17]

Geschickter and Copeland pointed out that the majority of their patients with carcinoma of the breast and secondary osseous involvement had had a radical amputation of the breast early in the disease, thus destroying many of the lymphatics which might have acted as a pathway for spread of the disease. They observed that relatively few of the osseous metastases were found in the vicinity of the primary tumor.

Geschickter and Copeland also pointed out that when the pelvic bones were involved there was not infrequently an associated invasion of the heads of the femurs. Gross and microscopic study in some of these cases showed direct involvement by means of the ligamentum teres, thus establishing proof that they may be an extension of a secondary tumor of one bone to another related bone via the lymphatics.

Thus, the evidence suggests that spread can take place to bones from primary sites via the blood stream and lymphatic system although when metastases occur in the jaw the spread is most likely to occur via the blood stream.

CLINICAL SIGNS AND SYMPTOMS OF METASTATIC CARCINOMA OF THE JAWS

Symptoms, when present, consist of pain of a severe rheumatic nature. There is often no apparent reason for this pain which occasionally precedes roentgenographic evidence of bony metastases by from three to eighteen months. The pain gradually increases in intensity, and eventually large amounts of drugs have to be administered to control it. When the mandible is involved, the earliest sign may be anesthesia over the peripheral distribution of the inferior dental nerve on the affected side. This symptom, in the absence of any other clinical findings, should always make one suspicious of a secondary neoplasm of the mandible. Pathologic fractures, especially of the long bones, are also a possible complication. In cases of extensive carcinomatous metastases there are, of course, such general symptoms as emaciation, pain, anemia, etc. No changes usually occur in the blood chemistry.

ROENTGENOLOGIC EXAMINATION

The roentgenographic appearance varies. An osteolytic lesion may be found in any part of the jaw, although, as stated earlier, it is most commonly seen in the molar region. In some cases the appearance may simulate osteomyelitis.

Although the reaction of bone to a metastatic tumor is exactly the same as that to a primary tumor, there are a few significant exceptions. Most metastases lead to bone destruction accompanied by a compensatory formation of bone. Metastases from scirrhous carcinoma of the breast very infrequently lead to an excessive formation of new bone and are therefore termed osteoblastic metastases as distinct from the more common osteoblastic metastases.

DIAGNOSIS

The history of a carcinoma of the breast, together with the clinical and roentgenographic signs mentioned, should make one suspicious of a metastatic lesion of the jaws. A biopsy is necessary, however, to provide definite proof of the presence of a metastatic lesion.

TREATMENT

The treatment of a secondary osseous tumor is confined to providing relief from pain and prolonging life; in other words, treatment is palliative in nature.

Irradiation produces relief from pain and sometimes accelerates repair in the affected bone, apparently temporarily reducing the invasive power of the tumor.

Mandibular resection is a mutilating operation which does not markedly prolong the life of the patient.

CASE REPORTS

A 61-year-old woman was admitted to the hospital with a pathologic fracture of the left femur. She was also complaining of a swelling of the right side of the mandible.

Past medical history revealed that a radical mastectomy for carcinoma of the breast had been performed several years previously. There was no local recurrence.

Radiographic examination showed a transverse fracture of the upper end of the left femur at the lesser trochanter level. At the site of the fracture there was a "moth-eaten" appearance suggestive of a destructive lesion in the middle of the cortex at both sides of the fracture, indicating the presence of a metastatic neoplasm.

While receiving treatment for the fractured femur, the patient complained of a painful swelling of the right side of the mandible.

Examination revealed a bony expansion of the right mandible involving a large portion of the horizontal ramus and extending beyond the angle into the vertical ramus (Figs. 1 and 2). There was an irregular destruction of the internal bony architecture with expansion of the cortex inferiorly and erosion of the alveolar border. There appeared to be irregular remnants of bony strands internally, producing a loculated effect not unlike the appearance of a central osteoclastoma. In view of the pathologic fracture of the left femur and the history of a radical mastectomy for carcinoma of the breast, a metastasis at an unusual site had to be considered.

A biopsy of the swelling of the mandible was performed under general anesthesia and submitted for histopathologic investigation. The pathologist reported that the section showed infiltration of bone by a scirrhous adenocarcinoma (Fig. 3). Secondary to a probable primary tumor in the breast.

The patient was referred for palliative radiotherapy.

Fig. 1.

Fig. 2.

Figs. 1 and 2.—Lateral oblique and anteroposterior roentgenograms of right mandible showing destruction at the angle.

SUMMARY

The incidence of metastases of carcinoma to bone and, in particular, the spread of primary carcinoma of the breast to the jaws are mentioned. Despite the frequency of skeletal metastases from primary carcinoma of the breast, few cases in which secondary deposits were found in the jaws have been reported. Some reasons for this infrequency are suggested.

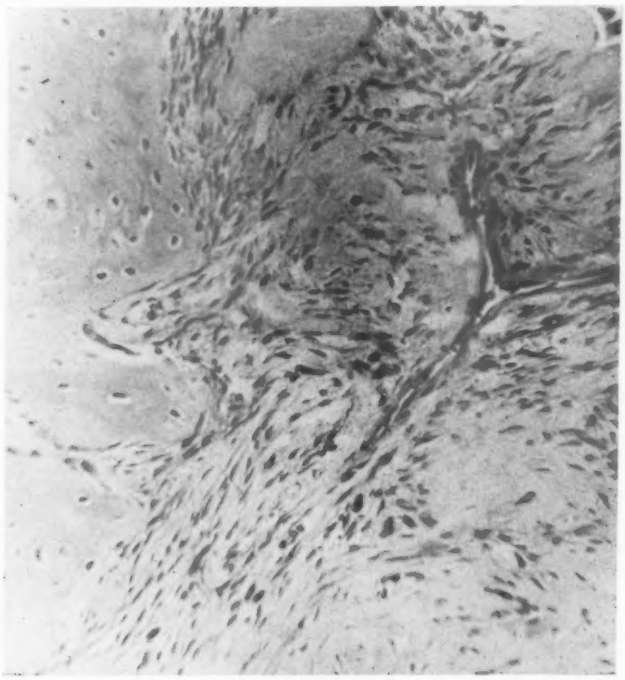

Fig. 3.—Section of tumor, low-power view. (Magnification, approximately ×200; reduced ⅙.)

The method of spread is discussed, and the views of various workers are mentioned, showing that the spread can take place via the blood stream and lymphatic vessels, the latter being of secondary importance in metastases to the jaws.

The signs, symptoms, roentgenographic appearances, and treatment are mentioned.

Finally, a further case of metastatic carcinoma of the mandible secondary to carcinoma of the breast is reported.

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TISSUE CHANGES IN THE PULP DURING EXPERIMENTAL LATHYRISM

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INTRODUCTION

LATHYRISM has been recognized in man and animals, particularly in India and North Africa.[1-3] This disease is caused by prolonged ingestion of a diet rich in *Lathyrus odoratus* seeds and involves lesions in the skeletal system and other mesenchymal tissues. The purpose of this investigation is to study the manifestations of experimental lathyrism in the dental pulp and to investigate the protective action of proteins and amino acids against experimental lathyrism.

In the literature[37-40, 44-62] on the dental pulp, it is frequently stated that the pulpal tissue should react differently from connective tissue in other areas of the body. It was therefore considered advisable to investigate the pulp's ability to react in a manner similar to or different from connective tissue in locations distant from the pulp.

The study of the reaction of the pulp to exogenous agents or influences presents a very complex problem. Regardless of the many facets involved, however, a knowledge of tissue changes in the pulp is very important if one is to obtain an insight into the pathogenesis of lathyrism and the many manifestations of the disease. In the past few years the major emphasis in experimental studies of the pulp has been on the influence of various cavity preparations as well as of various filling materials implanted in the dentine. These investigations have concentrated mainly upon comparisons of the pulpal

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response to local agents, that is, to different filling materials demonstrating the harmless or the harmful effects of the material in question.

This investigation is one of the few conducted in order to study the influence of systemic factors, as opposed to local factors, upon the tissues of the dental pulp. It appears necessary to establish the histologic picture of the normal control pulp before proceeding to the findings in the experimental pulp during lathyrism. A thorough search of the literature revealed no report on the histologic changes in the dental pulp of the rat or any other animal following experimental lathyrism.

REVIEW OF LITERATURE

The main symptoms of lathyrism in man are muscular weakness, with spastic paralysis of the lower extremities, and incontinence.

Stockman[1] was the first person who investigated experimental lathyrism in different species of animals. Following Stockman's initial findings, various effects of the lathyrus seeds in experimental animals were described. The seeds of different species of lathyrus produce different symptoms. Primarily, the production of the disease in the experiments that followed was due to the feeding of *Lathyrus odoratus* seeds to rats.[4, 5] Vivanco and Jimenez Diaz[6] believed that the syndrome caused by the feeding of *Lathyrus odoratus* to rats was not the same as the lathyrism reported in human beings.

Geiger and colleagues[7] reported that the initial changes due to *Lathyrus odoratus* diets in rats occurred in the skeleton, with kyphoscoliosis, thoracic deformation, and exostoses in the long bones, particularly at the insertions of muscles. These findings were confirmed by Lewis and associates.[8] Ponseti and Baird[9] were the first to investigate the changes in the skeleton during lathyrism, and they reported that *Lathyrus odoratus* diets caused dissecting aortic aneurysms and irregular proliferation of cartilage, especially at the growth plates.

Bachhuber and Lalich[10] confirmed these findings and have conducted histologic studies on aortic lesions. The pathogenesis of the skeletal changes has been investigated by Ponseti and Shepard.[11] Churchill and associates[12] reported that *Lathyrus odoratus* diets caused an alteration in the mucopolysaccharide of the ground substance of connective tissue in the aortic wall.

Bean and Ponseti[13] summarized the disturbances in mesodermal tissues due to the *Lathyrus odoratus* diet in rats and found that they were similar to idiopathic skeletal and aortic disturbances observed in man.

Dupuy and Lee[14] reported the isolation of a crystalline substance from the seeds of *Lathyrus pusillus,* which they found capable of producing lathyritic changes in the skeleton. A special material has been isolated from the seeds of *Lathyrus odoratus* and has been identified as beta-aminopropionitrile. Wawzonek and co-workers[15] were able to produce similar skeletal lesions through the feeding of beta-(gamma-L-glutamyl)-aminopropionitrile, aminoacetonitrile and bis-beta-cyanoethylamine. By adding beta-mercaptoethylamine to diets of rats, Dasler[16] was able to produce alterations in the skeleton similar to those produced by the lathyrus diet.

Although the active principle of the seeds of *Lathyrus odoratus* is beta-aminopropionitrile, aminoacetonitrile (the presence of which has not been shown in the seeds of *Lathyrus odoratus*) is more effective in producing skeletal lesions.

Ponseti and Shepard[17] report very briefly that resorption of the fetus occurs when pregnant rats are fed a *Lathyrus odoratus* diet. Pyörälä and colleagues[18] report that changes occur in the aorta and skeleton of the newborn rats whose mothers received a *Lathyrus odoratus* diet during pregnancy.

It is interesting to note that the skeletal reactions, whether they are due to diets rich in *Lathyrus odoratus* or to the subcutaneous administration of aminoacetonitrile, may be influenced at will by a variety of agents. Cortisol, ACTH, and thyroxin inhibit, while STH (somatotrophic hormone) and partial hepatectomy stimulate the skeletal reaction peculiar to experimental lathyrism.[19-26]

Oral, Maxillofacial, and Cranial Changes in Lathyrism.—The most important oral and cranial changes found in rats during lathyrism are periosteal new bone formations as unusually prominent exostoses at the sites of muscle insertions to the mandible and cranium. The most obvious oral manifestations are (1) exostoses at the coronoid, condyloid, and angular processes[27-29]; (2) gross bony deformities of the cranium and voluminous exostoses of the occipital bone[27]; (3) notching of the incisors and thus interference with the pattern of attrition[27, 30-32]; (4) increased ash content of incisors; (5) deformation of the mandible of *Amblystoma punctatum* embryos[33]; (6) hyalinization of the periodontal membrane[27-29]; (7) degenerative arthritis of the mandibular condyle[27-29]; (8) proliferation of connective tissue extending into the neighboring muscles inserting into the mandible; (9) osteoporosis of the alveolar process and ramus of the mandible; and (10) replacement of joint condylar cartilage by connective tissue.[27]

The gross manifestation of lathyrism is a skeletal change that affects the mandible of the experimental rat.[30] Spectacular skeletal changes may take place in the mandibles of rats on sweet-pea diets. When Dasler[30] fed a 50 per cent sweet-pea diet to weanling rats, exostoses developed on the ventral and lateral aspects of the mandible. The exostoses were palpable in all rats at the end of one week and became progressively worse. A disturbance in collagen metabolism or connective tissue metabolism was postulated. In 1954 Dasler[32] called attention to a notching of the incisors in growing rats fed sweet peas. He suggested that this notching is mechanical in origin, in that the overgrowth of bone in the proximal portions of the mandible probably limits the range of movement of the jaw and thus interferes with the normal attrition of the incisor.

Selye[34] found that with small doses of aminoacetonitrile, concurrent administration of somatotrophic growth hormone caused excessive growth and enamel defects in the incisors. The incisors showed marked malocclusion, with several horizontal enamel defects on the anterior surface and excessive growth in length. The tips of the upper incisors had turned upward and were growing into the palate and lips. The teeth often broke spontaneously.[34] In rats

receiving aminoacetonitrile plus cortisol[35] the mandible remained essentially normal, whereas voluminous mandibular exostoses developed in rats receiving aminoacetonitrile alone.

Krikos and associates[29] in 1958, reported upon oral tissues in rats fed a diet containing 0.2 per cent beta-aminopropionitrile. They found that in the regions of tendinous attachments the mandible developed exostoses characterized by a thick, highly cellular periosteum covering bone composed of thin trabeculae and broad marrow spaces. The mobility of the teeth was increased, and the condylar cartilage was enlarged. In the periosteum, fibroblastic proliferation leads to the appearance of osteoid matrix and bone. These phenomena are obviously reactive, but just what stimulus provokes them is still a controversial point. The stimulus is not hemorrhage, since no hemosiderin has been apparent. It is possible that the stimulus is the excessive ground substance itself.

EXPERIMENTAL MATERIALS AND METHODS

Introduction.—This research represents an investigation chiefly in microscopic morphology. Repeatedly in the history of lathyrism and related disorders, more has been expected of and claimed for morphologic changes than the methods could reasonably be expected to give.

It is believed that neither of the objectives that were most prominent in initiating this work is entirely beyond the scope of the methods used.

Rats.—The albino rat was chosen for this study for various reasons. It has been the experimental animal used most extensively in stress and hormone studies related to lathyrism. Moreover, the rat presents the additional advantage of being extremely susceptible to lathyrism. Another chief asset of the rat is the ease with which it can be fed different diets. The rat affords a tool for attack upon some of the great basic problems of aging. The rat also provides means for basic studies on bone changes with age. The great problem of why the bones of the rat are not permanently sealed at the epiphyses, even when the rat exceeds 1,000 days of age, remains unsolved. A dietary supplement of ascorbic acid is essential for the prevention of scurvy.[42, 43] This is of paramount importance since, radiographically, the skeletal lesions of lathyrism closely resemble scurvy. The rat was found to be especially favorable for this study because its incisors erupt relatively fast and show persistent growth and also because its molars resemble those of man in their gross and microscopic anatomy and in their limited growth.

Ninety-six male albino weanling rats of the Holtzmann-Sprague-Dawley strain, each weighing 45 to 50 grams, were used throughout this investigation. The rats were divided into groups at weaning and placed on various diets containing sweet peas. An additional group of male rats were pair-fed and served as normal littermate controls. Each of the experimental rats was paired with one of the normal controls of the same weight. The rats were housed in an open-bottom mesh cage. All control animals were sacrificed at the same time of day as the experimental animals. The rats were caged separately in an isolated room maintained at the usual laboratory temperature (70 to 80° F.). The

animals were weighed periodically, and their weight gains were recorded. Immediately after death, the rats were autopsied. The carcasses were skinned and eviscerated. The organs were examined for gross changes. The skulls were removed, x-rayed, and finally fixed in Zenker-formalin solution for one day or in Bouin's solution for two days. These fixatives were employed because they preserve the desired histologic details excellently, resulting in good morphologic differentiation. Individual teeth to be examined histologically were treated as described in the sections on histologic preparation and analysis.

Diets.—

Ground Lathyrus odoratus diets: The rats in the various groups were fed diets containing different amounts of *Lathyrus odoratus* and *Lathyrus odoratus* plus dietary supplements.

The *Lathyrus odoratus* diets were prepared by grinding the whole dry peas to a fineness which permitted all the pea meal to pass through a 24-mesh sieve. The dry ingredients were mixed separately and stored, cod-liver oil being added to portions of the mixture as needed.

The feedings were continued for different periods and consisted of the various experimental and control diets described in detail below. For control and experimental sweet-pea diets, the feedings were continued for one, two, and three weeks, respectively. For diets P.D. I to P.D. VII, the feedings were continued for fifty-six days.

It was known from pilot studies, that rats fed a given percentage of sweet peas in their diets will continue to survive only a certain period of time. Therefore, each group of rats was sacrificed in advance of this period, so that the data tabulated from the experimental groups would be uncomplicated by drastic terminal degenerative changes. Thus, all rats developed lathyrism but were still active.

The experimental diet (S.P. I, II, III) was as follows: *Lathyrus odoratus* meal, 50 per cent; casein,* 10 per cent; cornstarch, 25 per cent; sucrose, 5 per cent; brewers' yeast powder (dried), 4 per cent; salt mixture (Hubbell and associates[41]), 4 per cent; cod-liver oil, 2 per cent.

The control diets were as follows:

1. This control diet contained the same ingredients as the experimental diet, except that the *Lathyrus odoratus* meal was replaced by a 50 per cent dried and ground commercial edible pea meal.
2. Milled Rockland rat diet.

In this section of the present study, mixtures of dietary ingredients were fed in excess, together with *Lathyrus odoratus* meal, to determine whether they would enhance or suppress the development of lathyrism.

The basal diet (P.D. I) contained 30 per cent sweet-pea meal and 45 per cent cornstarch. Supplements were incorporated by replacing an equivalent amount of starch. All diets contained casein, gelatin, glutamine, or cysteine.

*Plain, untreated casein (not vitamin-free).

The protective diets (*Lathyrus odoratus* 30 per cent plus dietary supplements) were as follows:

P.D.* I: This was a control diet for all protective groups, no supplements being added. It consisted of ground sweet peas, 30 per cent; casein, 10 per cent; starch, 45 per cent; sucrose, 5 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

The following are experimental diets plus supplements (protective diets):

P.D. II: Ground sweet peas, 30 per cent; casein, 40 per cent; starch, 15 per cent; sucrose, 5 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

P.D. III: Ground sweet peas, 30 per cent; gelatin, 25 per cent; sucrose, 5 per cent; starch, 30 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

P.D. IV: Ground sweet peas, 30 per cent; casein, 35 per cent; glutamine, 5 per cent; cysteine hydrochloride, 4 per cent; sucrose, 5 per cent; starch, 11 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

P.D. V: Ground sweet peas, 30 per cent; casein, 10 per cent; glutamine, 5 per cent; sucrose, 5 per cent; cysteine hydrochloride, 4 per cent; starch, 36 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

P.D. VI: Ground sweet peas, 30 per cent; casein, 10 per cent; sucrose, 5 per cent; cysteine hydrochloride, 4 per cent; starch, 41 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

P.D. VII: Ground sweet peas, 30 per cent; casein, 10 per cent; glutamine, 5 per cent; starch, 40 per cent; sucrose, 5 per cent; brewers' yeast, 4 per cent; salt mixture,[41] 4 per cent; and cod-liver oil, 2 per cent.

Histologic Preparation and Analysis.—After sacrifice and fixation, the upper and lower jaws were dissected free from the skulls, so that tissue sections consisted of upper molars, upper incisors, lower incisors with lower molars. These were embedded separately in individual blocks.

Mediodistal sections through two buccal roots of the upper and lower molars, buccolingual sections of the upper and lower molars, sagittal sections of the upper and lower incisors, and frontal sections of total intact hemisections of skulls were prepared for sectioning, mounting, and staining by the various methods employed in this investigation.

*P.D. is used as an abbreviation for protective diets.

After at least twenty-four hours in the fixative, the tissue sections were decalcified. The procedure used for decalcification of mineralized tissues for collagen from bone and teeth utilized ethylenediaminetetraacetic acid (EDTA) which has a pH of 7.0. All material was decalcified for six days in EDTA to effect the best staining.

To overcome any processing inadequacies and artifacts, a paraffin-celloidin double-embedding method was utilized. This slowed down the progression to absolute alcohol and prolonged the treatment in celloidin-methyl benzoate to three days, with the final paraffin treatment being limited to four to six hours.

All histologic sections were cut consecutively at 6 to 8 microns and stained with hematoxylin and eosin, Wilder's stain, and Mallory's phosphotungstic acid-hematoxylin stain. After mounting in Canada balsam, the coverslips were weighted down so that flat sections might be obtained.

HISTOLOGIC FINDINGS

In order that the alterations occurring in the pulpal connective tissues might be fully evaluated, a brief description of the normal histology will be given.

Control Pulp.—The pulp of control rats is a specialized type of loose connective tissue. The histology of the control pulp stained with hematoxylin and eosin may be described as follows: The pulp consists of a zone immediately adjacent to the calcified dentine which is termed the predentine zone. It is usually eosinophilic in its staining reaction, but under certain circumstances it may appear unstained. The predentine zone is distinguishable from the adjacent odontoblastic layer of the pulp by a well-demarcated pulpodentinal membrane. In the odontoblastic layer there exists a highly differentiated connective tissue with cells arranged in a parallel manner along the pulpodentinal membrane and bordering the predentine. The odontoblasts are tall columnar cells in the crown, low columnar in the mid-root, and more or less spindle shaped in the apical third of the root. They contain an oval nucleus, which is evenly stained and does not contain nucleoli in mature odontoblasts. Pulpward to the odontoblastic layer is the cell-free zone of Weil. Blood vessels are abundant and easily identifiable in the zone of Weil. Proceeding toward the central area of the pulp from this cell-free zone of Weil is an area containing a larger concentration of cells than are present in the central zone of the pulp. This is termed the cell-dense zone.

The central portion of the pulp contains a number of cellular elements that vary according to anatomic location. It consists of fibroblasts and gelatinous intercellular material. The substance between the fibroblasts consists of an irregular network of collagenous fibers and a cementing substance. In addition to the fiibroblasts, the pulpal tissue contains other mesenchymal cells of importance. Undifferentiated spindle-shaped mesenchymal cells are present as defensive cells of the reticuloendothelial system and are located in the central portion as well as along the course of blood vessels. These are the macrophages of the pulp. Other macrophages (histiocytes) are usually present at locations distant from blood vessels. Lymphoid wandering cells may be scattered throughout the pulp and are capable of transformation into macrophages.

The fibrils of the pulp are partly precollagenous and partly collagenous. The amorphous ground substance forms a continuous mass, and the pulp is the only connective tissue in the body that has no interstitial spaces.

Argyrophilic (Korff's) fibers are also present in the pulp. They form thick bundles passing between the odontoblasts. They are visible only by silver impregnation. The central portion of the pulp is also abundantly supplied with blood vessels and nerves (Fig. 1).

In advancing age, the cellular elements of the pulp are decreased, whereas the fibrous components are increased in number.

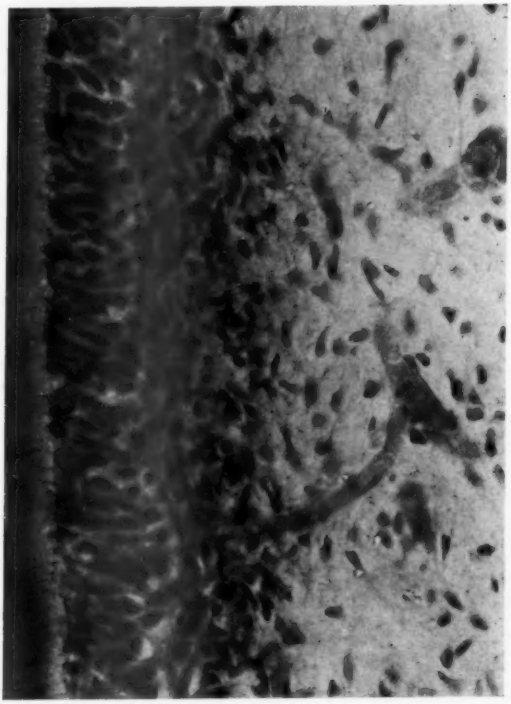


Fig. 1.—Photomicrograph of the molar pulp of a littermate control animal fed a Rockland rat diet for three weeks. (Hematoxylin and eosin stain. Magnification, ×600; reduced ⅝.)

Experimental Molar Pulp After Eight Weeks of Protective Diets (Table 1).—At the termination of the experimental period with protective diet I containing no protein or amino acid supplementation, eosinophilic zones occurred in the molar pulp (Fig. 2). These consisted of circular zones surrounding the walls of small blood vessels and appearing as irregularly distributed areas throughout the central portion of the pulp. They appeared as areas showing a stronger eosinophilic staining, which was in sharp contrast to the lighter-stained adjacent pulpal tissue. The perivascular zone was due possibly to the diffusion of

eosinophilic protein material through the capillary wall into the ground substance. It is possible that the beta-aminopropionitrile (BAPN) content of the sweet pea may act as a capillary poison. This eosinophilic zone, composed of a possible serous exudate, may be regarded as a criterion of pulpal reaction. However, there is no real conclusive evidence for the exact cause of the eosinophilic diffusion during lathyrism.

TABLE I. COMPARISON OF CHANGES IN THE PULP OF MOLARS IN MALE RATS FED LATHYRITIC DIETS PLUS PROTECTIVE SUBSTANCES FOR EIGHT WEEKS

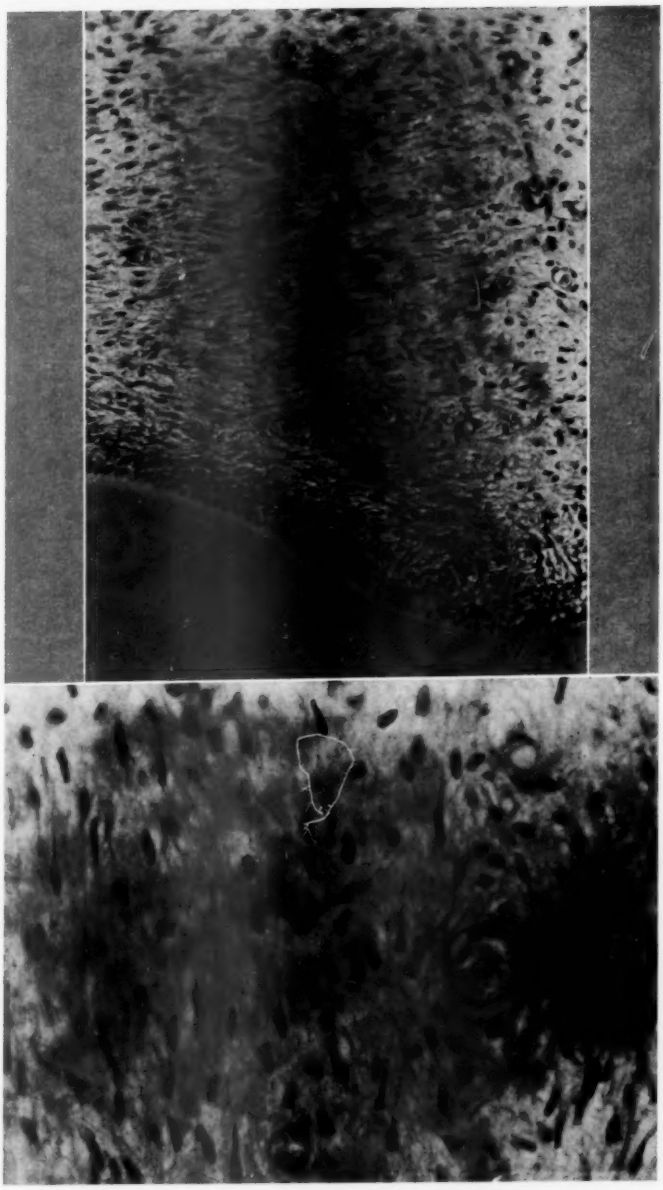
PROTECTIVE DIET GROUP	EOSINOPHILIC ZONES	CAVITY FORMATIONS IN ODONTOBLASTIC LAYER	CAVITY FORMATIONS CENTRALLY IN PULP	VACUOLES IN ODONTOBLASTS	NUCLEOLI IN ODONTOBLASTIC NUCLEI	CAPILLARIES IN ODONTOBLASTIC LAYER	EXTRAVASATED ERYTHROCYTES
P.D. I	+	+	+	–	+	++	–
P.D. II	–	–	–	–	–	–	+
P.D. III	–	–	–	–	–	–	–
P.D. IV	–	–	–	–	–	–	+
P.D. V	–	+	–	–	–	–	–
P.D. VI	–	+	–	–	–	–	–
P.D. VII	–	–	–	–	–	+	+

PROTECTIVE DIET GROUP	HYPEREMIA	ODONTOBLASTIC NUCLEI IN DENTINAL TUBULES	PRESENCE OF INFLAMMATORY CELLS IN ODONTOBLASTIC LAYER	PRESENCE OF INFLAMMATORY CELLS CENTRALLY IN PULP	CALCIFICATIONS AND DENTICLES IN RADICULAR PULP	CELLULAR INVASIONS, DENTIFICATIONS, CALCOSPHERITES	HYALINE METAPLASIA, EOSINOPHILIC MATERIAL IN PULP
P.D. I	+	+	–	–	–	+	+
P.D. II	+	–	–	–	–	–	–
P.D. III	–	–	–	–	+	–	–
P.D. IV	+	–	–	–	–	–	–
P.D. V	–	–	–	–	–	–	–
P.D. VI	–	–	–	–	–	–	–
P.D. VII	+	–	–	–	–	–	–

P.D. = Protective diet.
+ = Present.
– = Absent.

Small cavity formations and vacuoles were observed in the odontoblastic zone, in Weil's zone, and in the cell-rich zone. These empty spaces were located between the cells of the odontoblastic zone as well as in their cytoplasm (intercellular and intracellular edema). It appears that edema is one of the reactions in the pulp during lathyrism, inasmuch as empty spaces were present surrounding the pulpal cells principally throughout the coronal pulp. It is also possible that hyaline degeneration occurred, accompanied by atrophy of the pulp. The vacuoles located between the odontoblasts may be due to exudation of lymph. However, nucleoli were present in odontoblastic nuclei. Chromatin scattered throughout nuclei and nucleoli is usually present only in odontoblasts of teeth in a developmental stage, whereas nuclei of normal mature odontoblasts are homogeneous dark bodies in which neither chromatin nor nucleoli appear. It may be that preodontoblasts have invaded the damaged odontoblastic layer. Nucleoli in odontoblasts, however, cannot be considered a decisive criterion for determining the age of odontoblasts.

A.



B.

Fig. 2.—*A*, Photomicrograph of the molar pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weks. Note the eosinophilic zones, which were irregularly distributed throughout the pulp, in proximity to the blood vessels. They are darker areas contrasting sharply with the normal adjacent pulpal tissue. (Hematoxylin and eosin stain. Magnification, ×180; reduced ⅝.)

B, High-power view of the eosinophilic zone shown in Fig. 2. (Hematoxylin and eosin stain. Magnification, ×550; reduced ⅝.)

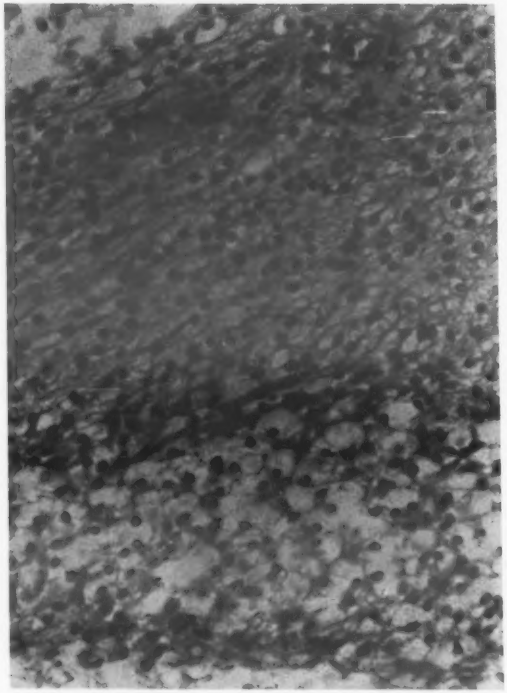


Fig. 3.

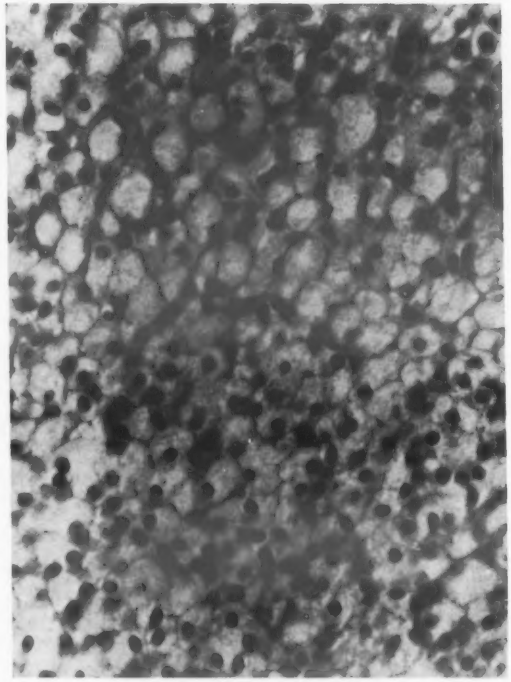


Fig. 4.

Fig. 3.—Photomicrograph of the molar pulp of a male rat fed a 50 per cent sweet-pea diet for three weeks. Note the cavity formations in the odontoblastic layer. They appear as empty spaces located between the cells of the odontoblastic zone as well as in the cytoplasm (intercellular and intracellular edema). (Hematoxylin and eosin stain. Magnification, ×600; reduced ⅝.)

Fig. 4.—Photomicrograph of the molar pulp of a male rat fed a 50 per cent sweet-pea diet for three weeks. Note the cavity formations centrally in the coronal pulp. This accumulation of material causes the cells to increase to several times their normal size. The round nucleus is centrally located, and the cytoplasm gives a clear cell reaction. (Hematoxylin and eosin stain. Magnification, ×750; reduced ⅝.)

Capillaries were present in the odontoblastic zone of the pulp (Figs. 6 and 18). They appeared as minute capillaries among the odontoblasts as well as adjacent to the predentine. They formed numerous loops close to the odontoblastic zone and proliferated into the odontoblastic layer itself. These capillaries

Fig. 5.

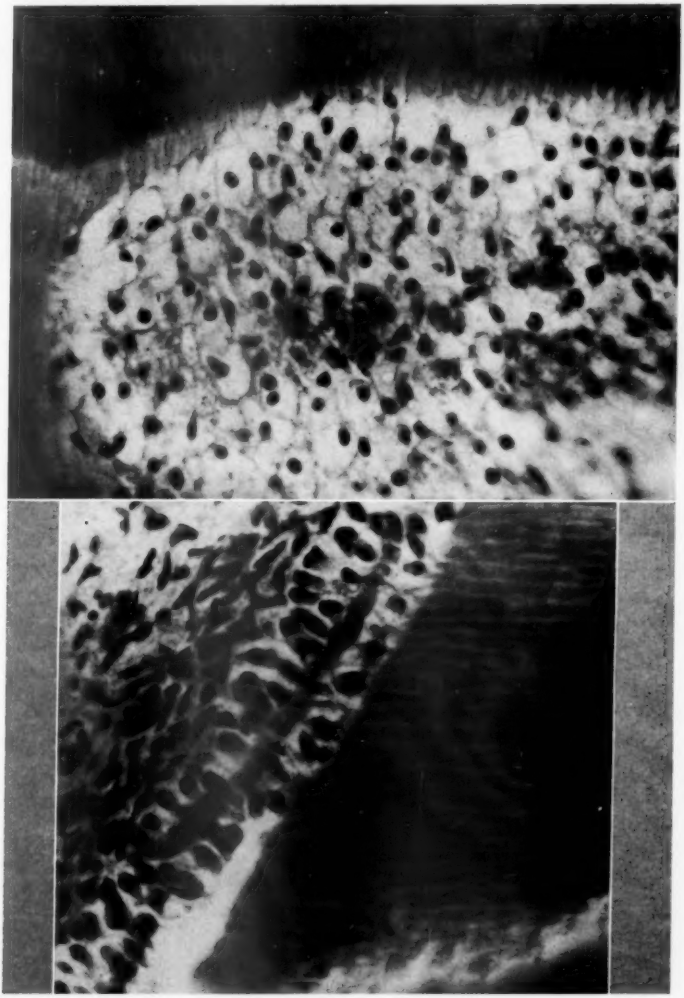


Fig. 6.

Fig. 5.—Photomicrograph of the molar pulp of a male rat fed a 50 per cent sweet-pea diet for three weeks. Note vacuolization in the cytoplasm of the odontoblasts (vacuolar degeneration). (Hematoxylin and eosin stain. Magnification, ×750; reduced ⅔.)

Fig. 6.—Photomicrograph of the molar pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the presence of capillaries in the odontoblastic zone. They appear as minute new formations of capillaries among the odontoblasts as well as adjacent to the predentine. (Hematoxylin and eosin stain. Magnification, ×750; reduced ⅔.)

are new formations, since their presence was never seen in the littermate control animals. This hyperproduction of capillaries is important evidence of a reaction in the pulp of rats fed the lathyrus toxin without the dietary protein and amino acid supplementation which inhibits this proliferation. In some areas of the pulp of animals fed protective diet I, a few ruptured capillaries were observed within the odontoblastic layer with slight extravasation of erythrocytes.

The capillaries in the central portion of the pulp of this group were more clearly evident than in any of the protective diet groups with protein and amino acid supplementation. This is evidently because of the degree of hyperemia present (Fig. 8). The advanced hyperemia is probably due to the fact that the circulation of blood was impaired through some degenerative change which was on the chemical level such as a proximal chemical lesion and not demonstrable morphologically. In the early stage of hyperemia, the blood vessels are dilated and engorged. Hemorrhages were absent in rats fed protective diet I. The criterion for hemorrhage was the presence of extravasated erythrocytes or the presence of brown pigment, both of which are diagnostic in demonstrating hemorrhages.

In several instances in the group fed protective diet I eosinophilic, darkly stained, nucleus-like bodies were found in the dentinal tubules (Fig. 15). These are odontoblastic nuclei that have occasionally migrated into the dentinal tubules. Odontoblastic nuclei deteriorate after entering the dentinal tubules. The mechanism involved in the migration of the odontoblastic nuclei into the tubules has not been clarified in this study, or in other previous investigations. All one can conclude is that cell nuclei occasionally penetrate the dentinal tubules, but no acceptable explanation of this phenomenon can be given from the results of this investigation.

There were no inflammatory cells in the odontoblastic layer or centrally in the pulp (Fig. 14). Calcifications, calcific degeneration, and denticles were absent in all rats of this group. Cellular invasions were present in the pulps of rats fed protective diet I, within the predentine zone as well as replacing degenerated odontoblasts in the odontoblastic zone.

Hyaline metaplasia appeared within the odontoblastic zone in the apical region (Fig. 10). These zones or bodies consisted of eosinophilic material located between the odontoblasts and the adjacent zone. They appeared as areas of degenerated odontoblasts and pulpal cells. In the areas where degeneration of odontoblasts occurred, an irregular calcified tissue or cellular dentine was formed. The dentine was atypical, being nontubular with cellular inclusions. There were foldings and projections of dentine into the pulp.

In the protective diet II group, which received protein and amino acid supplementation, the eosinophilic zones that were formed in the protective diet I group were now absent. Moderate hyperemia was still evident, but to less marked degree with respect to the number of vessels involved and the degree of dilatation present. A mild degree of hemorrhage occurred, with localized areas of extravasated erythrocytes present in the coronal pulp.

The following pathologic findings were absent in the pulp of this group: (1) cavity formations, (2) vacuoles in odontoblasts, (3) nucleoli in

Fig. 7.

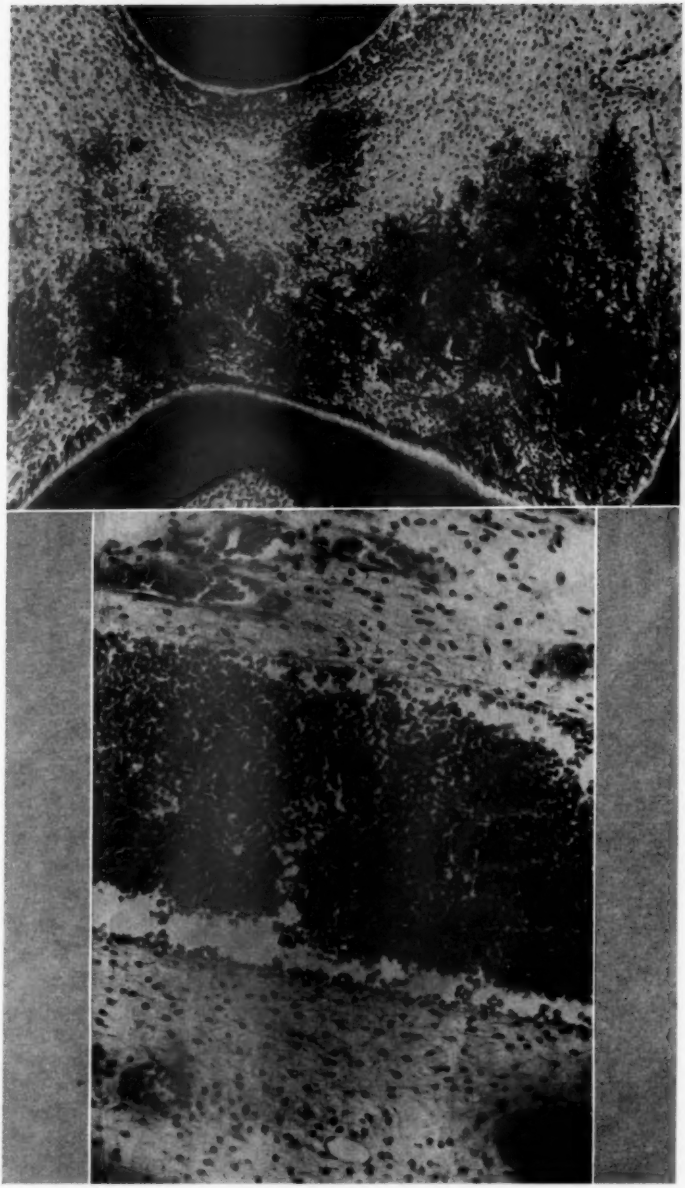


Fig. 8.

Fig. 7.—Photomicrograph of the molar pulp of a male rat fed a 50 per cent sweet-pea diet for three weeks. Note massive exudation of red blood cells due to an increase in permeability of capillaries. The hemorrhage occupied approximately one-fourth of the coronal portion invading the odontoblastic zone. (Hematoxylin and eosin stain. Magnification, ×100; reduced ⅝.)

Fig. 8.—Photomicrograph of the molar pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the more clearly evident capillaries in the central portion of the pulp. This is due to hyperemia of pulpal vessels because of impairment to the circulation of blood. (Hematoxylin and eosin stain. Magnification, ×200; reduced ⅝.)

Fig. 9.

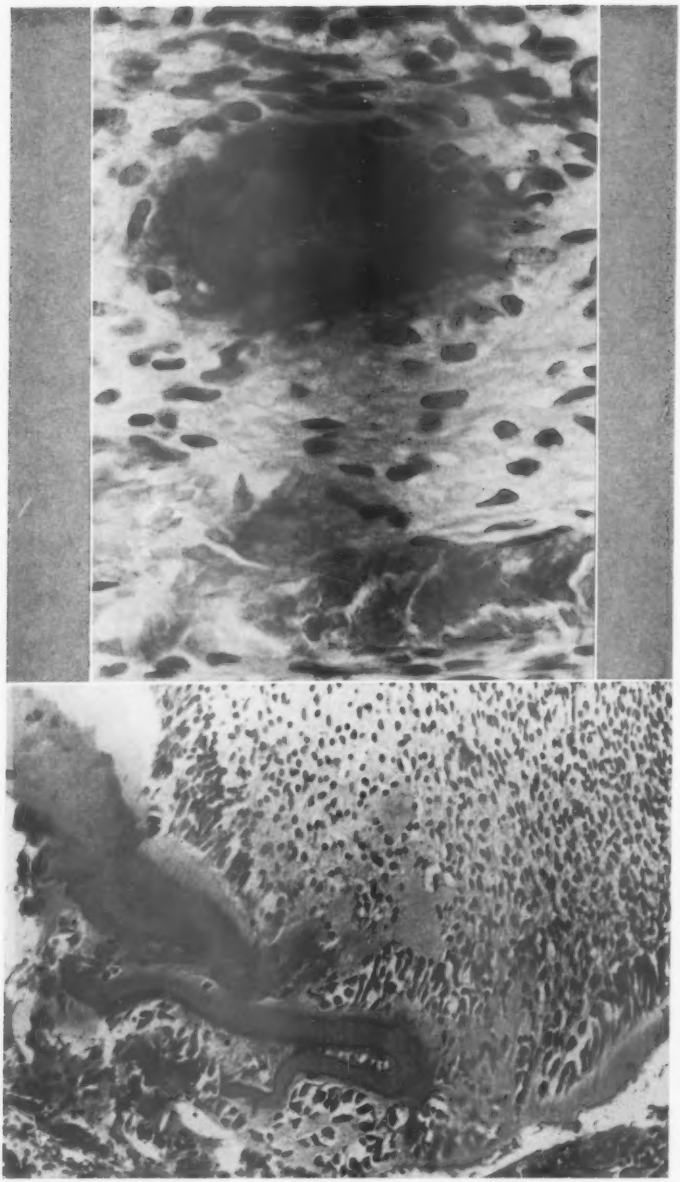
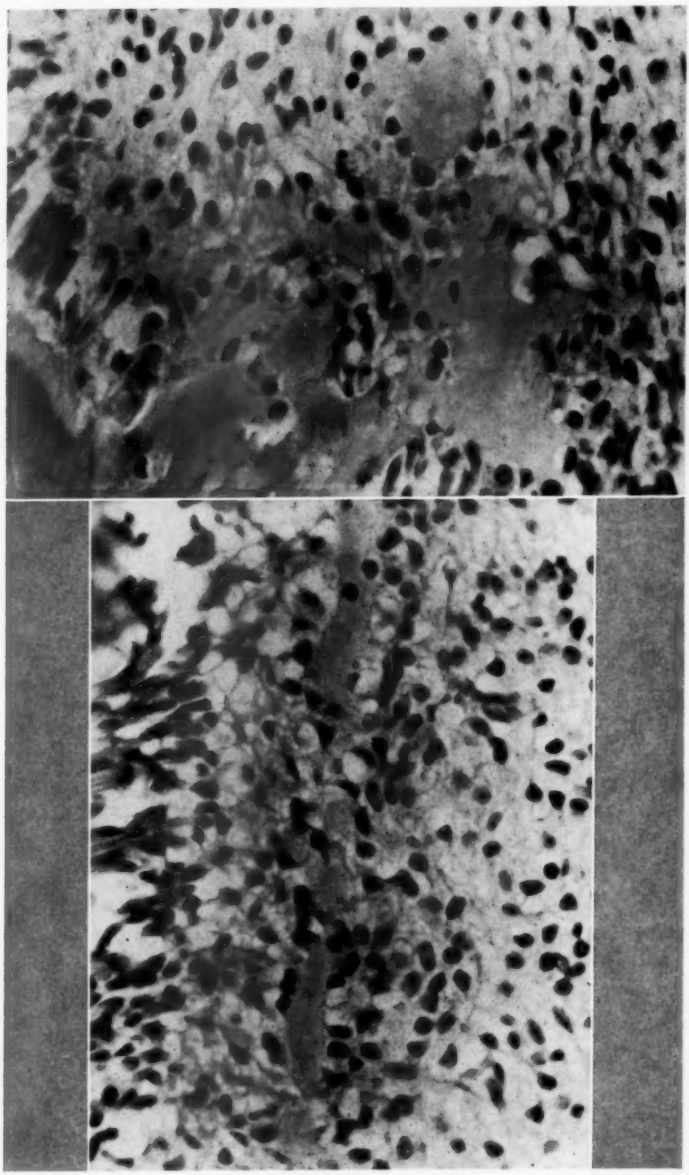


Fig. 10.

Fig. 9.—Photomicrograph of the molar pulp of a male rat fed protective diet III (protein and amino acid supplementation). Note calcification in the radicular pulp of the mesial root. It is located close to fiber bundles and blood vessels. This calcification is a false denticle consisting of layers or zones of different degrees of calcification without a dentinal structure. (Hematoxylin and eosin stain. Magnification, ×800; reduced ⅔.)

Fig. 10.—Photomicrograph of the incisor pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the hyaline metaplasia at the basal third of the incisor (the most rapidly growing or germinal zone). These areas are small and irregular in shape, or they may extend as a long, narrow, eosinophilic, wavy band between groups of pulpal fibroblasts (Fig. 11, *B*). They are composed of eosinophilic material accumulating in the intercellular substance (lathyritic bodies). (Hematoxylin and eosin stain. Magnification, ×180; reduced ⅔.)

A.



B.

Fig. 11.—*A*, High-power view of eosin-stained area in Fig. 10. (Hematoxylin and eosin stain. Magnification, ×550; reduced ⅝.)

B, High-power view of long and narrow eosinophilic wavy material accumulating intercellularly between groups of pulpal fibroblasts in another area of the same pulp shown in Fig. 10. (Hematoxylin and eosin stain. Magnification, ×520; reduced ⅝.)

odontoblastic nuclei, (4) capillaries in odontoblastic nuclei, (5) odontoblastic nuclei in dentinal tubules, (6) presence of inflammatory cells, (7) calcifications and denticles, (8) dentifications, cellular invasion, and calcospherites, and (9) hyaline metaplasia in odontoblastic and adjacent zone.

In animals fed protective diet III, calcification occurred in the radicular pulp. These calcifications were irregular in shape and were located close to fiber bundles, blood vessels, and nerves (Fig. 9). These calcifications are false

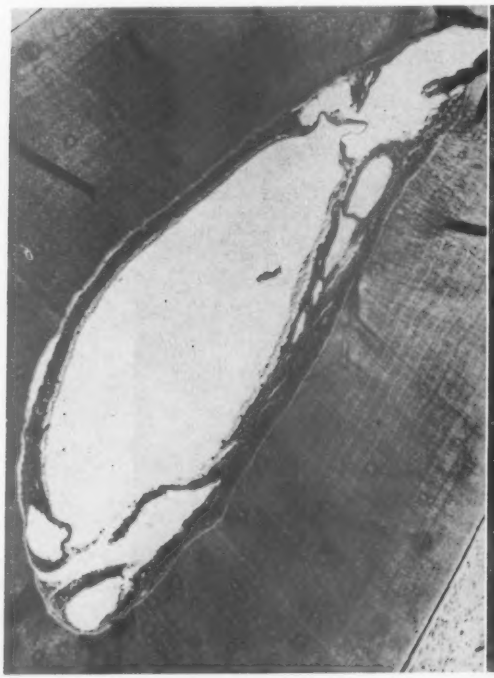


Fig. 12.

Fig. 13.

Fig. 12.—Photomicrograph of the anterior zone of the incisor pulp of a male rat fed a 50 per cent sweet-pea diet for three weeks. Note the large cystic cavity occupying the major portion of the pulp. The only pulpal tissue remaining consists of a deeply stained eosinophilic membrane or cyst wall lining the cystic cavity and bordering the dentine. (Hematoxylin and eosin stain. Magnification, ×90; reduced ⅝.)

Fig. 13.—High-power view of the cystic wall shown in Fig. 12. (Hematoxylin and eosin stain. Magnification, ×750; reduced ⅝.)

denticles consisting of layers or zones of different degrees of calcification without a dentinal structure or pattern. No pathologic changes were observed, either in cells or in intercellular fibrous matrix. The cell nuclei between the fiber bundles were spindle shaped and darkly stained.

The following experimental findings were absent in this group: (1) eosinophilic zones, (2) cavity formations, (3) vacuoles in odontoblasts, (4) nucleoli in odontoblastic nuclei, (5) capillaries in odontoblastic layer, (6) extravasated

erythrocytes, (7) odontoblastic nuclei in dentinal tubules, (8) presence of inflammatory cells, (9) dentifications, cellular invasions, and calcospherites, and (10) hyaline metaplasia in odontoblastic and adjacent zone.

In the rats fed protective diet IV, hemorrhages were a common finding and were present only in the coronal pulp. Extravasated erythrocytes were observed, but only to a mild degree. The following experimental findings were absent in this group: (1) eosinophilic zones, (2) cavity formations, (3) vacuoles in odontoblasts, (4) nucleoli in odontoblastic nuclei, (5) capillaries in odontoblastic layer, (6) odontoblastic nuclei in dentinal tubules, (7) presence of inflammatory cells, (8) dentifications, cellular invasions, and calcospherites, and (9) hyaline metaplasia in odontoblastic and adjacent zone.

In the group fed protective diet V, cavity formations occurred within the odontoblastic layer. Separation of the odontoblasts, vacuoles among the odontoblasts, degeneration of odontoblasts, and edema were noted. The following experimental findings were absent in this group: (1) eosinophilic zones, (2) vacuoles in odontoblasts, (3) nucleoli in odontoblastic nuclei, (4) capillaries in odontoblastic layer, (5) odontoblastic nuclei in dentinal tubules, (6) presence of inflammatory cells, (7) dentifications, cellular invasions, and calcospherites, and (8) hyaline metaplasia in odontoblastic and adjacent zone.

In the animals fed protective diet VI with protein supplementation, vacuolization of the odontoblastic zone was still present. The cavity formation or empty spaces developed in the ground substance. The following experimental findings were absent in this group: (1) eosinophilic zones, (2) nucleoli in odontoblastic nuclei, (3) vacuoles in odontoblasts, (4) capillaries in odontoblastic layer, (5) odontoblastic nuclei in dentinal tubules, (6) presence of inflammatory cells, (7) dentifications, cellular invasions, and calcospherites, and (8) hyaline metaplasia in odontoblastic and adjacent zone.

In the animals fed protective diet VII, there were loops of capillaries present in the odontoblastic layer due to hyperproduction and proliferation.

Extravasated erythrocytes were also found in this group. They retained their usual form and, like intravascular erythrocytes, they stained a bright red with hematoxylin and eosin. They occurred as aggregates in rouleaux, in clusters, and singly. They occurred particularly in the central portion of the coronal pulp, but they were also found scattered throughout pulp tissue and appeared in the odontoblastic layer. The erythrocytes were apparently unchanged extravascularly as well as intravascularly.

There was hyperemia of the vessels throughout the pulp. They contained blood cells tightly packed within the vessel lumen. There was, however, no evidence of stasis or thrombosis. Pigment formation was absent in this group.

In spite of the fact that brown pigment has not been identified in the the lathyritic pulp, the diagnosis of hemorrhage is justified. The absence of brown pigment simply signifies that the extravasated erythrocytes represent an early hemorrhage. Deterioration products may have been removed by fluids or macrophages in those animals devoid of hemorrhage or pigment. The following experimental findings were absent in this group: (1) eosinophilic

Fig. 14.

Fig. 15.

Fig. 14.—Photomicrograph of the molar pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the absence of inflammation in the odontoblastic layer and centrally in the pulp. (Hematoxylin and eosin stain. Magnification, ×275; reduced ⅝.)

Fig. 15.—Photomicrograph of the molar pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the darkly stained odontoblastic nuclei or nucleus-like bodies in the dentinal tubules. (Hematoxylin and eosin stain. Magnification, ×600; reduced ⅝.)

zones, (2) cavity formation, (3) vacuoles in odontoblasts, (4) nucleoli in odontoblastic nuclei, (5) odontoblastic nuclei in dentinal tubules, (6) presence of inflammatory cells, (7) dentifications, cellular invasions, and calcospherites, and (8) hyaline metaplasia in odontoblastic and adjacent zone.

Experimental Molar Pulps After One, Two, and Three Weeks of 50 Per Cent Sweet-Pea Diets (Table II).—At the termination of one week of a 50 per cent nonsupplemented sweet-pea diet, eosinophilic zones were not distinguishable at the periphery of the pulp in the area adjacent to the odontoblasts.

TABLE II. COMPARISON OF CHANGES IN THE PULP OF MOLARS IN MALE RATS FED LATHYRITIC DIETS (SWEET PEA) WITHOUT PROTECTIVE SUBSTANCES FOR ONE, TWO, AND THREE WEEKS RESPECTIVELY

SWEET PEA GROUP	EOSINOPHILIC ZONES	CAVITY FORMATIONS		VACUOLES IN ODONTOBLASTS	NUCLEOLI IN ODONTOBLASTIC NUCLEI	CAPILLARIES IN ODONTOBLASTIC LAYER	EXTRAVASATED ERYTHROCYTES
		IN ODONTOBLASTIC LAYER	CENTRALLY IN PULP				
S.P. I	–	–	–	–	–	+	–
S.P. II	+	–	–	–	–	++	+
S.P. III	+	+	+	+	–	+	++
Control	–	–	–	–	–	–	–

SWEET PEA GROUP	HYPEREMIA	ODONTOBLASTIC NUCLEI IN DENTINAL TUBULES	PRESENCE OF INFLAMMATORY CELLS		CALCIFIC DEGENERATION IN RADICULAR PULP	CELLULAR INVASIONS, DENTIFICATION, CALCOSPHERITES	CELLULAR DEGENERATION, RETICULAR ATROPHY OF PULP
			IN ODONTOBLASTIC LAYER	CENTRALLY IN PULP			
S.P. I	–	–	–	–	–	–	–
S.P. II	+	–	–	–	–	–	–
S.P. III	+	–	–	–	+	–	+
Control	–	–	–	–	–	–	–

S.P. = Sweet pea.

Capillaries were observed as minute loops among the odontoblasts, reaching as far as the predentine border. These small loops were not numerous but were generally dotted throughout the entire odontoblastic layer. The presence of these capillaries among the odontoblasts is evidence of hyperproduction of capillaries.

The following experimental findings were absent in this group of rats: (1) cavity formation, (2) vacuoles in odontoblasts, (3) nucleoli in odontoblastic nuclei, (4) extravasated erythrocytes, (5) odontoblastic nuclei in dentinal tubules, (6) presence of inflammatory cells, (7) dentifications, cellular invasions, and calcospherites, and (8) hyaline bodies in odontoblastic and adjacent zone.

In the group of rats fed a 50 per cent nonsupplemented sweet-pea diet for two weeks, a very small eosinophilic zone bordered the dentine at the periphery of the pulp. Capillaries were generally more numerous with an abundance of capillary loops which were readily visible within the odontoblastic layer. Dilated and hyperemic capillaries were present adjacent to the cell-free zone of Weil. In the central portion of the pulp, extravasated erythrocytes were found; this was considered diagnostic of hemorrhage. The following experimental findings were absent in this group: (1) cavity formation, (2) vacuoles

in odontoblasts, (3) nucleoli in odontoblastic nuclei, (4) odontoblastic nuclei in dentinal tubules, (5) presence of inflammatory cells, (6) dentifications, cellular invasions, and calcospherites, and (7) hyaline bodies in odontoblastic and adjacent zone.

At the termination of three weeks of the 50 per cent nonsupplemented sweet-pea diet (S.P. III), the following experimental conditions developed: A distinct eosinophilic zone was present along the pulp periphery. This zone was distinguishable at the periphery of the pulp in the area adjacent to the odontoblasts and showed a stronger eosinophilic staining than the rest of the pulp. Eosinophilic areas were also present in the central portion of the pulp. These occurred surrounding the walls of small blood vessels. They were spherical areas that stained eosinophilic as compared to the lighter pulpal tissue surrounding them.

In the cells of the odontoblastic layer and in the central portion there was an accumulation of material which caused the cells to increase to several times their normal size (Fig. 5). The nucleus was round and more or less centrally located. The cytoplasm had a clear, vacuolated appearance with distinct cell outlines. The clear cell reaction within the fibroblasts of the pulp occurred predominantly in the coronal portion (Fig. 4). The odontoblasts surrounding the degenerated pulpal fibroblasts were disrupted and had also undergone similar retrograde changes. The changes in the odontoblastic zone consisted of different degrees of degeneration from simple disorganization and vacuolar degeneration to disappearance of odontoblasts with cavity formation (Fig. 3). Between these extremes, tremendous cellular edema and hydropic degeneration occurred in the subodontoblastic layer. The edematous changes are the forerunners of hyaline degeneration and necrosis of pulpal cells. In the main, the pulpal tissue in the major portion of the crown showed a diffuse degenerative clear cell reaction. The cellular architecture was disrupted, with the presence of a peculiar homogeneous intercellular material. As a result, the pulpal tissue in some areas had a netlike appearance.

Initially, the pulp reaction was turgescent. Later, massive exudation of red blood cells occurred as the result of an increase in permeability of capillaries. The extravasation of erythrocytes was massive and occupied approximately one-fourth of the coronal portion invading the odontoblastic zone (Fig. 7). Hemorrhages were also present in the subodontoblastic zone. Several areas of profuse or massive hemorrhage were noted in the central area of the pulp, as though vessels had ruptured. The number of blood vessels and nerves is greatly reduced, particularly in the atrophic zones. Fluid-containing spaces, surrounded by fibers of the pulp, were frequently present. These spaces, which varied from small round areas to larger zones, may have been due to a localized pulpal atrophy occurring with shrinkage of the pulp tissue.

Several areas of calcific degeneration were present in the radicular pulp of this group. They consisted of concentric layers of calcified material, and the deposits were present in areas not approximated by degenerated foam cells.

Capillaries proliferated into the odontoblastic zone only in the areas in which the cells had not disappeared; however, capillary invasion was not as prominent as in the group fed sweet-pea diet II.

The following experimental findings were absent in this group: (1) nucleoli in odontoblastic nuclei, (2) odontoblastic nuclei in dentinal tubules, (3) presence of inflammatory cells, and (4) dentifications, cellular invasion, and calcospherites.

Experimental Incisor Pulps After Eight Weeks of Protective Diets (Table III).—At the termination of eight weeks of a nonsupplemented lathyritic diet (P.D. I), the incisor pulp was gradually decreased in size and was partially dentinified in the anterior zone as a result of the retardation in eruption.

TABLE III. COMPARISON OF CHANGES IN THE PULP OF INCISORS IN MALE RATS FED LATHYRITIC DIETS PLUS PROTECTIVE SUBSTANCES FOR EIGHT WEEKS

PROTECTIVE DIET GROUP	EOSINOPHILIC ZONES	CAVITY FORMATIONS		VACUOLES IN ODONTOBLASTS	NUCLEOLI IN ODONTOBLASTIC NUCLEI	CAPILLARIES IN ODONTOBLASTIC LAYER	EXTRAVASATED ERYTHROCYTES
		IN ODONTOBLASTIC LAYER	CENTRALLY IN PULP				
P.D. I	–	–	–	–	+	++	–
P.D. II	–	–	–	–	–	–	–
P.D. III	–	–	–	–	+	+	–
P.D. IV	–	–	–	–	+	–	–
P.D. V	–	–	–	–	+	+	–
P.D. VI	–	–	–	–	–	+	–
P.D. VII	+	–	–	–	–	+	–

PROTECTIVE DIET GROUP	HYPEREMIA	ODONTOBLASTIC NUCLEI IN DENTINAL TUBULES	PRESENCE OF INFLAMMATORY CELLS		CALCIFICATIONS, CALCIFIC DEGENERATION, AND DENTICLES	DENTIFICATIONS, CELLULAR INVASION, CALCOSPHERITES	HYALINE OR EOSINOPHILIC BODIES IN PULP
			IN ODONTOBLASTIC LAYER	CENTRALLY IN PULP			
P.D. I	+	+	–	–	–	+	+
P.D. II	–	–	–	–	–	–	–
P.D. III	+	–	–	–	–	–	–
P.D. IV	–	–	–	–	–	–	–
P.D. V	+	–	–	–	–	–	–
P.D. VI	+	–	–	–	–	–	–
P.D. VII	+	–	–	–	–	–	–

P.D. = Protective diet.
+ = Present.
– = Absent.

The pulpal surface facing the enamel-covered sides showed a distortion of form. A wavelike border occurred along the odontoblastic surface. This border presented four large folds, with several minor folds between the more prominent ones. In the basal zone the pulp took on a somewhat typical appearance; it was richly cellular in comparison with the control material. The pulps had developed an eosinophilic zone at the periphery, along the dentine border, and perivascularly in the central portion of the pulp. The intercellular substance appeared homogeneous and excessive in quantity at the basal end of the pulp (Fig. 11).

With Wilder's stain, increased deposition of collagen-like material (lathyritic body) was noted at the basal end of the pulp (Fig. 16). With Mallory's

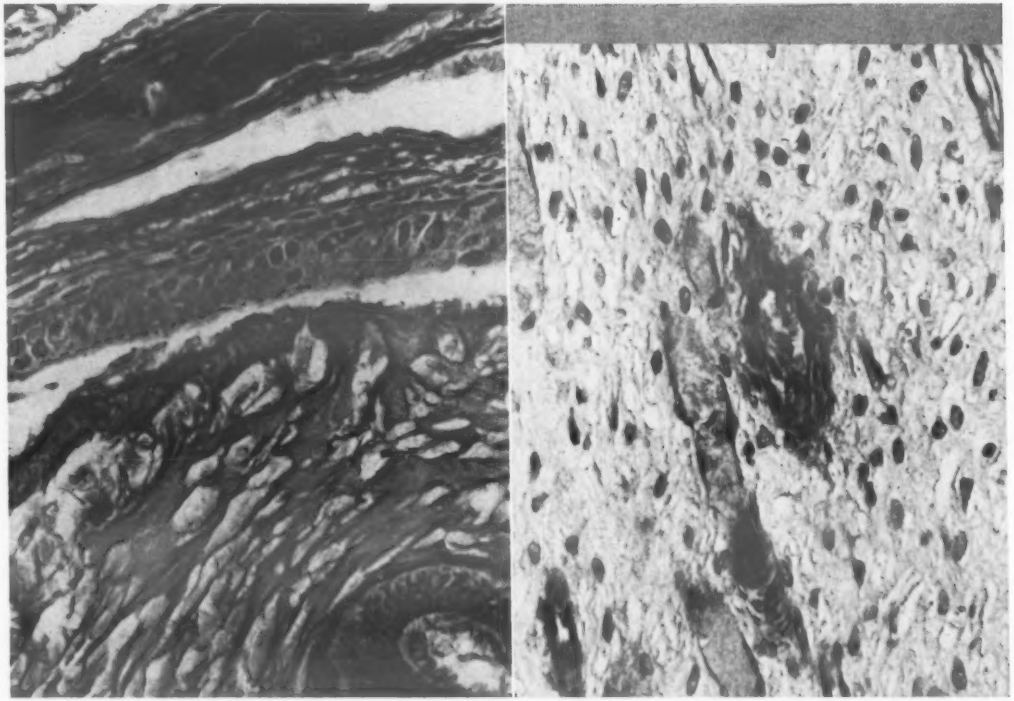


Fig. 16. Fig. 17.

Fig. 16.—Photomicrograph of the incisor pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the increased deposition of a collagen-like material between pulpal fibroblasts at the basal end of the pulp. (Wilder's stain. Magnification, ×800; reduced ⅜.)

Fig. 17.—Photomicrograph of the incisor pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the increased deposition of a collagenous material which is frequently found adjacent to capillaries. (Mallory's phosphotungstic acid-hematoxylin stain. Magnification, ×600; reduced ⅜.)

phosphotungstic acid-hematoxylin stain, dense collagen concentrations were found surrounding capillaries of the pulp, particularly at the basal end (Fig. 17).

Nucleoli were present in odontoblastic nuclei, odontoblastic nuclei were present in dentinal tubules, and numerous capillary loops had proliferated into the odontoblastic layer adjacent to the predentine. Hyperemia of the pulp was also evident.

At the basal third of the incisor, hyaline metaplasia (lathyritic bodies) developed within the odontoblastic layer as well as in Weil's zone and adjacent zones close to the odontoblasts. These areas were either small and irregular in

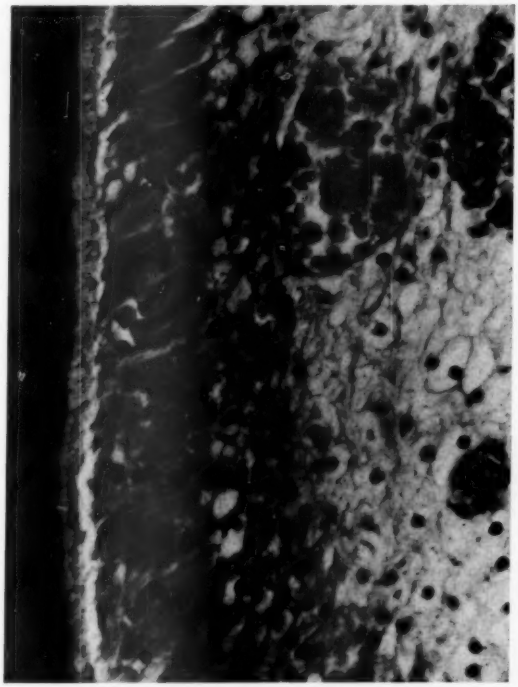


Fig. 18.—Photomicrograph of the incisor pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the capillaries invading the odontoblastic zone. They appear as new formations of capillaries adjacent to the predentine. (Hematoxylin and eosin stain. Magnification, ×750; reduced ⅝.)

shape or extended as a narrow eosinophilic wavy band between pulpal fibroblasts. They were composed of eosinophilic material accumulating in the intercellular substance (lathyritic body). The eosinophilic material was consistently confined to the basal or germinal area of the incisor.

The basal dentine produced in the area adjacent to the eosinophilic material showed an irregular outline with a wavelike disturbance at the dentinocemental junction. Because of the continued formation and apposition while eruption was delayed, the outline of the newly formed roots of the incisor presented a

heaping-up and folding of the dentine instead of a smooth dentinal surface. This occurred frequently in the upper incisor but was not present in the lower incisor. This irregular dentinal outline occurred only toward the basal end and involved the younger odontoblasts. On the lingual aspect there was an accumulation of dark eosin-staining material next to Hertwig's sheath. Histochemical studies revealed that this material was increased collagen.

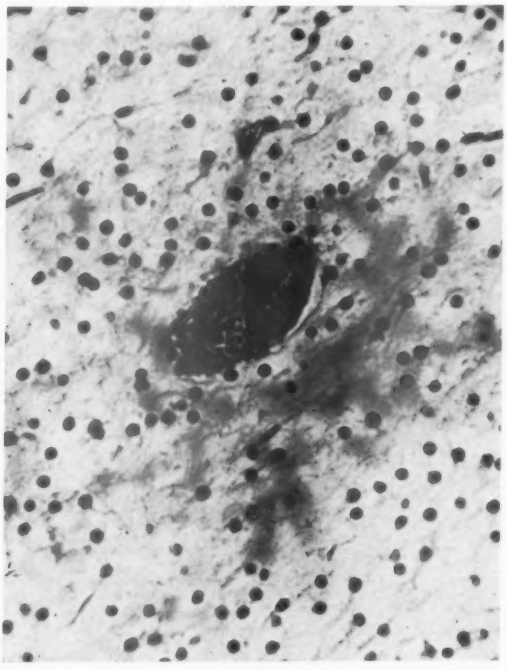


Fig. 19.—Photomicrograph of the incisor pulp of a male rat fed protective diet I (30 per cent nonsupplemented sweet peas) for eight weeks. Note the densely stained eosinophilic zones in proximity to a blood vessel. The eosinophilic zones are sharply contrasted with the normal adjacent pulpal tissue. (Hematoxylin and eosin stain. Magnification, ×500; reduced ⅝.)

At the termination of protective diet II (protein and amino acid supplementation) the incisor pulp was greater in size when compared to that subjected to protective diet I. The pulp was free of the changes enumerated for P.D. I, the well-demonstrated eosinophilic material. The severe folding of the dentine at the base of the incisor was now a smooth surface in the newly formed root. In animals fed protective diet III the pulp contained nucleoli in odontoblastic nuclei. Capillaries were present in the odontoblastic layer, but they were not as numerous as in the animals fed protective diet I. Hyperemia was present, but no hemorrhage occurred. The dentine on the pulpal aspect was smooth with a regular outline.

The group fed protective diet IV showed incisor pulps with nucleoli in odontoblastic nuclei. All other experimental findings were negative.

Protective diet V produced hyperemic pulps, with capillaries invading the odontoblastic layer, and nucleoli were present in odontoblastic nuclei. The eosinophilic zone along the dentine was absent. In rats fed protective diet VI capillaries had proliferated into the odontoblastic layer, with hyperemia in the remaining portion of the pulp. The eosinophilic zone was absent.

In the animals fed protective diet VII a few giant cells were present in the incisor pulp. They were probably formed from macrophages. The macrophage may be found as fixed cell elements or as rounded ameboid cells. Under the toxic lathyrus influence, these cells may have been transformed into giant cells. Hyperemia and capillaries in the odontoblastic zone were present in this group.

Experimental Incisor Pulps After One, Two, and Three Weeks of Sweet-Pea Diets Without Supplementation (Table IV).—At the completion of one week of a 50 per cent nonsupplemented sweet-pea diet, hyperemia was the main finding observed in the incisor pulp. Eosinophilic zones were not apparent.

TABLE IV. COMPARISON OF CHANGES IN THE PULPS OF INCISORS IN MALE RATS FED LATHYRITIC DIETS WITHOUT PROTECTIVE SUBSTANCES FOR ONE, TWO, AND THREE WEEKS, RESPECTIVELY

SWEET PEA GROUP	EOSINOPHILIC ZONES	CAVITY FORMATIONS		VACUOLES IN ODONTOBLASTS	NUCLEOLI IN ODONTOBLASTIC NUCLEI	CAPILLARIES IN ODONTOBLASTIC LAYER	EXTRAVASATED ERYTHROCYTES
		IN ODONTOBLASTIC LAYER	CENTRALLY IN PULP				
S.P. I	–	–	–	–	–	+	–
S.P. II	–	–	–	–	–	+	+
S.P. III	+	+	+	+	+	+	++
Control	–	–	–	–	–	–	–

SWEET PEA GROUP	HYPEREMIA	ODONTOBLASTIC NUCLEI IN DENTINAL TUBULES	PRESENCE OF INFLAMMATORY CELLS		CALCIFICATIONS, CALCIFIC DEGENERATION, AND DENTICLES	DENTIFICATIONS, CELLULAR INVASIONS, CALCOSPHERITES	HYALINE BODIES OR EOSINOPHILIC MATERIAL IN PULP
			IN ODONTOBLASTIC LAYER	CENTRALLY IN PULP			
S.P. I	–	–	–	–	–	–	–
S.P. II	+	–	–	–	–	–	–
S.P. III	+	–	–	–	+	–	+
Control	–	–	–	–	–	–	–

S.P. = Sweet pea.
+ = Present.
– = Absent.

After two weeks of the 50 per cent sweet-pea diet, capillaries had begun to proliferate and invade the odontoblastic layer. The capillaries were seen as small loops among the odontoblasts as well as bordering the predentine. Hyperemia with dilatation of blood vessels was prominent in most areas of the pulp. Eosinophilic zones were not present along the dentinal border of the pulp.

In the group of rats fed a 50 per cent sweet-pea diet for three weeks, the incisor pulp showed very prominent vessels due to hyperemia and dilatation. In this group numerous hemorrhages occurred, particularly between the dentine

and the odontoblastic layer. The hemorrhages first became conspicuous after three weeks, as evidenced by extravasated erythrocytes in the center of the pulp as well as between the odontoblasts. Eosinophilic areas were prominent along the dentine borders and in perivascular locations.

In the incisal third of the lower incisor, the pulp showed a massive necrosis with cystic degeneration. A large cystic cavity occupied the major portion of the pulp. The only pulpal tissue remaining consisted of deeply eosinophilic-stained membrane lining the central cavity and bordering the dentine (Figs. 12 and 13). There was complete cessation of the formation of any kind of dentine in this incisal region. The odontoblasts became morphologically indistinguishable from the other cells of the pulp that may have remained in the compressed membrane. This cystic degeneration was absent in the upper incisor. In the middle and basal thirds of the lower incisor pulp, as well as in the pulp of the upper incisor, capillaries were very numerous and had proliferated with the formation of many loops between the odontoblasts and predentine. The odontoblasts were present but appeared disorganized and disrupted. Hydropic degeneration of pulpal fibroblasts had occurred, and some nuclei had disappeared. However, the reaction in the lower incisor was much more severe in the incisal third, which was probably due in part to the abnormal pattern of attrition as well as to the sweet-pea toxin.

DISCUSSION

Scope of Impairment in Lathyrism.—The impairment and injury that occur to connective tissues in lathyrism are of a selective form. The toxic portion of the sweet pea, that is, the metabolized beta-aminopropionitrile in the diet, shows an affinity for one particular tissue (mesenchymal tissue). Thus, it exerts a selective toxicity. This selective injury, however, is further complicated by early divergent co-injury.

In tissues subjected to stress, the changes in the connective tissue elements became more prominent (as in the periodontal ligament) than in the more protected connective tissues (pulpal connective tissue). The protected connective tissues were also subjected to numerous changes, even though the degree of change was not as severe as in connective tissues under greater stress. Therefore, two factors appear operative in lathyritic lesions: (1) the sweet-pea toxin and (2) the presence of some stress factor. Both are necessary in order for the most severe alterations to occur in connective tissues. Concentrating upon the dental pulp, it has been shown that lesions of lathyrism, which are common to all mesodermal structures, also occur in the pulpal connective tissue with a general breakdown of supporting elements.

The damage inflicted in lathyrism is proportional to the intensity or quantity of the sweet pea as well as to the presence of dietary supplements consumed by the rats, compounded by the duration of exposure. Due initially to the proliferative and subsequent degenerative changes in the mandibular growth cartilage, coinjury disturbs the normal pattern of attrition of the incisors and molars. This coimpairment spreads to the incisors because of the

physiologic interdependence between the incisor and the condylar process of the mandibular ramus. The relationship between intensity of injury and degree of damage can be summarized by stating that the lesser quantity and the shorter period of experimental sweet-pea feeding, with and without protective substances, tend to produce impairment of a reversible nature, whereas large quantities fed for long periods of time tend to produce irreversible impairment with destruction of pulpal tissues of the animals.

In this investigation, the 50 per cent treatment dose given for one week produced a stimulating effect in the rats fed sweet peas. After two weeks there was a depressive effect, and after three weeks there was a destructive effect because of the cumulative impairment (quantity plus duration) in addition to the fact that the agent of injury is additive.

The diet which contained 50 per cent sweet pea, when fed to weanling rats for three weeks, caused a 115 per cent increase in body weight in the experimental animals as compared to a 229 per cent increase in the control animals. This represented approximately a 60 per cent inhibition of growth.

It is entirely probable that all the various disorders described in lathyrism have a common pathogenesis, since they can all be produced by diets containing sweet peas. Ponseti and Shepard[9, 17] believe that all of these lesions are due to a defective formation or an excessive destruction of the chondroitin sulfate of the ground substance, since all lesions occur in areas containing chondroitin sulfate as the main mucopolysaccharide. This must be further substantiated. Menzies and Mills[36] believe that the fundamental change is excessive accumulation of intercellular ground substance which has a strong affinity for metachromatic toluidine blue but reacts weakly with periodic acid-Schiff stain (PAS). With this accumulation of chondroitin sulfate, the general breakdown of supporting structures such as collagen fibrils, takes place. They identified by site and staining reaction the intercellular material which appears strongly metachromatic but PAS negative as chondroitin sulfate. Thus, there is an important connection between the lathyrus factor and the sulfated mucopolysaccharides. Churchill and colleagues[12] agree with the above findings concerning the increase of metachromatic mucopolysaccharide which is PAS negative and which they conclude to be chondroitin sulfate B.

It is premature at this writing to attempt a conclusion as to the definite mechanism in the pathogenesis of lathyrism. Nonspecific stress may play a role, with the lathyrus factor only a predisposing element. Hormone balance and hepatic function are conditioning factors for the response to the actual lathyritic factor.

Eosinophilic Zones.—Previous investigators believe that eosinophilic staining along the dentine is generally a sign of blood plasma diffusing from capillaries.[40] This theory may apply to lathyrism, since in this experiment the sweet-pea toxin may have injured the capillary walls with the result that an exudate accumulated in the tissues. Although this capillary injury occurred days before the rats were sacrificed, the exudate did not appear to be organized or stain like fibrils.[37] Whether fibrin was formed and removed by enzymes in

this area is not known. It is difficult to evaluate whether or not the eosinophilic zone constitutes a definite and specific pulpal reaction due to the lathyrus toxin. Even though it cannot be considered specific for lathyrism, however, it may still indicate some change in the pulp due, among other things, to the *Lathyrus odoratus* toxin.

Cavity Formation.—Cavity formation and vacuolization were present throughout the pulp due to disaggregation of the ground substance. Both the vacuolization of the odontoblastic layer and the pulpal atrophy were characterized by a decrease in the number and size of pulpal cells and their replacement by fibers. In lathyrism there is a degeneration of the ground substance, and this is manifested in the vacuolization of the pulp.

Vacuoles in Odontoblasts.—This investigation did not evaluate the contents of vacuoles in the odontoblasts. They occurred only after three weeks of ingestion of a 50 per cent sweet-pea diet and in animals fed protective diet VII. This finding is no doubt due to hydropic degeneration.

Nucleoli in Odontoblastic Nuclei.—Previous investigators[38, 39] have observed nucleoli in odontoblastic nuclei and believe that mature odontoblasts contain homogeneously dark nuclei and that the odontoblastic nuclei in teeth are the result of a developmental stage in which clearly scattered chromatin and nucleoli are present.

The lathyrus diet without supplements showed prominent nucleoli which may be the reaction of the pulp to lathyrus toxin. In the reaction area (odontoblastic layer) the toxin causes an invasion by young odontoblasts due to damage to this odontoblastic layer. The young cell replacing the former mature odontoblast contains nucleoli.

This effect is not due to extraction or drilling, since these operations were not performed. At the present time, however, it is difficult in this investigation to consider the presence of nucleoli in odontoblastic nuclei as a mandatory criterion in determining the age of odontoblasts.

Capillaries in the Odontoblastic Layer.—Large numbers of capillaries were found in sections of pulps in the rats fed protective diet I without supplements and in all the groups fed the 50 per cent sweet-pea diets (S.P. I, II, and III). This appears to be evidence of hyperproduction of capillaries. After a period of one week only a few capillary loops were present in the odontoblastic layer. This capillarization increased so that at three weeks, and again at eight weeks, the production of capillaries was exceedingly numerous. This disturbance could not be caused by such factors as injection of local anesthetics or luxation, since all such trauma was avoided in this investigation. Therefore, it seems plausible that the lathyrus toxin causes abnormal production of capillaries.

Extravasated Erythrocytes and Hyperemia.—The extravasated erythrocytes that were found in the pulp were considered a criterion of hemorrhage. The extravasation of erythrocytes is hypothesized as a reaction to the sweet-pea toxin. No organization of blood pigment occurred. It is possible that beta-aminopropionitrile is a capillary poison and that its influence leads to

dilatation of capillaries and hemorrhages by the process of diapedesis. This hypothesis seems plausible, since hemorrhage is a very common finding in damaged mesodermal tissue.

Odontoblastic Nuclei in Dentinal Tubules.—In lathyrism, when no protective substances are added to the diet, occasional odontoblastic nuclei may migrate into dentinal tubules. The mechanism by which the nucleus migrates has not been established. It may be due to chemotaxis or pressure.

Presence of Inflammatory Cells.—Inflammatory cells were consistently absent in the odontoblastic layer, in Weil's zone, and in the remaining areas of the pulp, indicating that in lathyrism the toxin does not provoke an inflammatory response but produces a direct retrograde change.

Calcifications in the Pulp.—In the present investigation, calcifications were observed in pulps of rats fed a 50 per cent sweet-pea diet for three weeks and in the pulp of animals fed protective diet III which contained gelatin and glutamine. In all instances the calcification and denticles were formed in the radicular pulps. They were not related to calcification of vessel walls, since neither pulp vessels nor vessels elsewhere in the body showed calcification. Pulp vessels, therefore, react in a manner similar to vessels in other tissues of the body. The denticles were solid and free of spaces, and the connective tissue of the pulp was in contact with the calcification, implying some adhesion between surrounding tissue and denticle. The calcifications appear unrelated to the lathyrus toxin.

Cellular Invasions.—Cellular invasions were evident in the molar pulps of only one group of rats (protective diet I). These invasions occurred in the radicular pulp; the odontoblasts were replaced and the dentine was invaded. All other groups were free of dentifications, cellular invasion, or calcospherites. Even the group of rats fed 50 per cent sweet peas was free of cellular invasions after three weeks. Therefore, more than three weeks is required for the production of cellular inclusions.

Cellular Degeneration and Hyaline Bodies.—The pulp of animals fed sweet-pea diet III presented the appearance consistent with intracellular edema after three weeks of a 50 per cent sweet-pea experimental diet. This atrophy, with an accompanying decrease in the matrix, may be a result of hydropic degeneration. The pulpal tissue appeared in the form of a tissue network, with cavity formation present in the coronal portion. The odontoblasts were either missing, degenerated, or incomplete. The pulp was poor in vessels and nerves. There were a few groups of remaining odontoblasts.

This atrophy with accompanying degenerative changes may be looked upon as an aging process of the pulp tissue. It required three weeks for this to occur after the rats were initially placed upon the 50 per cent sweet-pea diet.

In contrast to the cellular degeneration and atrophy of the pulp in the S.P. III experimental group (50 per cent sweet pea), the pulp of the group fed protective diet I (30 per cent sweet pea for eight weeks) showed localized areas of eosinophilic material within the odontoblastic zone.

The cellular degeneration occurred only in the pulps of molars and did not involve the incisors of sweet-pea-fed animals. However, in protective diet I group, without supplements, the hyaline bodies occurred in both molar and incisor pulps. This is no doubt due to the extended period of treatment in the protective diet group, since this group was fed for an additional five weeks. The deceleration of eruption present in lathyrism is therefore due to the primary destructive effects of the fast-growing basal end of the pulpal connective tissue. The eruptive force of the incisor is probably derived from the activity of the proliferating odontogenic epithelium and the pulpal cells. Thus, it can be shown that the degenerative material in these pulps readily prevents the pulp from exercising its part of the eruptive force.

That vascularity of the pulp is a factor in an accelerated eruption rate does not seem entirely true, according to the results of this investigation. Along with the decreased eruption rate during lathyrism, there is a very vascular pulpal bed. The increased local vascularity and tissue fluid content apparent in most of the experimental pulps do not indicate any correlation between the dental vascular bed and eruption. This does not prove, however, that vascularity has no part in the eruptive force within the jaws. It appears that vascularity, if it does take place in eruption, serves in a minimal way. Essentially, the behavior of the growth center is the vital factor. In lathyrism, although vascularity is prominent, the degenerative change in the connective tissue of the growth center prevented the pulp from exerting its eruptive potential and effecting normal extrusion from the jaw.

The influence of stress upon the eruption rate during lathyrism is not clear. The stress factor in lathyrism is assumed to be a systemic manifestation which may be acting upon the attritional function of the incisors, directly upon the eruptive force within the jaws, or a combination of both. Knowledge of the superimposition of stress upon eruption rate in this experiment obscures any interpretation of the protective diet and sweet-pea treatments and may present a factor heretofore not taken into account in previous eruption studies in which stress was a component part of the experiment.

Differences in Reaction of Molar and Incisor Pulps During Lathyrism.— The changes enumerated in Tables I to IV occurred earlier and were more pronounced in the pulpal tissue of the molars than in the pulp of the incisors. This held true for the protective diet groups as well as for the nonsupplemented sweet-pea groups. This may be considered as due to the fact that the mechanism of growth is different in these two teeth. In the molar the pulp is of limited growth, and the growth center diminishes its activity after the molar has fully erupted. In contrast, the incisor pulp is of continuous growth, and its growth center normally does not alter its potential since eruption is constantly occurring. Thus, this rapid renewal of tissue allows the incisor to repair itself, therefore minimizing the pulpal damage at an early stage. With prolonged feeding, however, the growth center of the incisor is sufficiently altered to impede eruption.

Influence of Dietary Substance on Pulpal Changes During Lathyrism.—All animals of the protective groups with dietary substances (protein and amino acids) added to their diets failed to develop the hyaline necrosis or bodies present in the odontoblastic layer of animals fed protective diet I (the control nonsupplemented group). Cellular invasions were similarly lacking in all experimental protective diet groups (P.D. II to P.D. VII). The degree of hyperemia was less in animals fed protective diets II, III, V, VI, than in the controls (P.D. I). These diets contained casein, gelatin, glutamine, and cysteine. Hyperproduction of capillaries was prevented in all protective diet groups except those fed P.D. VII, and in this group the capillaries were not as numerous as in the group given P.D. I. Nucleoli were absent in the odontoblastic nuclei in all protective diet groups. The eosinophilic zones surrounding blood vessels were likewise absent, so that exudation from capillaries was not prominent in the protective diet groups.

Protein Supplementation in Lathyrus Diets.—The usefulness of dietary protein, so far as the animal is concerned, depends on the amount but also on the nutritional value. Adequate protein supplementation is that which supplies the desired kind and quantity of amino acids essential to the normal physiology and growth of the animal. Dietary rations that fall short of this requirement are considered inadequate. In this investigation, adequate semipurified rations containing sweet peas were given ad libitum to weanling rats; varying the proportion of dietary casein, gelatin, and amino acids had an influence on body weight. Actually, the rats ingesting the higher protein rations are, on the average, heavier than animals fed a nonsupplemented diet. Thus, during lathyrism rats can maintain normal body weight if allowed free access to proteins and amino acids, even if the efficiency of utilization may possibly be decreased. Under the same experimental conditions of lathyrism, rats fed lower proportions of proteins and amino acids do not grow as well. Casein in proportions of 30 to 40 per cent or more may be considered adequate to prevent the onset and reduce the severity of experimental lathyrism. Gelatin in proportions of 25 per cent may also be considered adequate to prevent the symptoms of lathyrism.

The results and interpretations of this investigation concerning the utilization of dietary proteins and amino acid should separate a discussion into (1) the consequences of varying the proportions of proteins in lathyrus diets, within limits adequate for growth and (2) the effects of nonsupplemented lathyrus diets.

Proportions of Protein Supporting Normal Body Weight.—The incidence and rate of appearance of the lathyritic body which is specific for experimental lathyrism varied significantly among groups of rats which were fed, ad libitum, semipurified lathyrus diets containing 10 or 40 per cent casein. In some groups on the lowest protein levels, small but significant effects would be exhibited upon the lathyritic lesion. The results obtained might have been expected, however, since most of the tissues of the animal were affected in size by variations within this range.

When the experimental animals received either 40 per cent casein or 25 per cent gelatin rations, there was a striking inhibition of lathyritic body formations in the pulp.

The addition of 25 per cent gelatin, which is actually an inadequate protein, still significantly prevented the high incidence of lathyritic bodies prevalent in rats fed the nonsupplemented lathyrus diets. In contrast, supplementing the 10 per cent casein with glutamine and cysteine decreased the incidence of lathyritic bodies to that observed among rats on a 10 per cent casein-supplemented lathyrus diet. The proportion of sulfur-containing amino acids in casein is actually a somewhat limiting factor in the nutritive value of casein, and its biologic potentiality is raised by supplementation with glutamine and cysteine. The addition of 5 per cent glutamine and 4 per cent cysteine no doubt produces a diet nutritionally equivalent to perhaps approximately twice that of 10 per cent casein alone, since the number of lathyritic bodies is slightly more than in animals fed the 40 per cent casein-supplemented lathyrus diet. It is likely that the inhibitory effect on lathyritic body formation was due to an increase in balanced protein if augmented by supplementary glutamine and cysteine. Therefore, the induction of lathyritic bodies in rats fed *Lathyrus odoratus* seeds depends on a number of dietary features, one of these being the proportion of protein. Increasing the dietary protein or improving the biologic value of casein by supplementation with amino acids has been shown by this investigation to have an inhibitory influence on the genesis of the lathyritic change. The outcome, however, may be dependent upon other features of the ration. The resultant concentration of riboflavin in the liver is enhanced by high dietary protein,[63, 64] and it is not unlikely that it is depressed on ingestion of *Lathyrus odoratus* seeds. It is doubtful whether the beneficial effects of dietary proteins and amino acids in rats fed the *Lathyrus odoratus* seeds involve the critical beta-aminopropionitrile reaction. It is more probable that they represent merely another example of the ability of dietary protein to increase the resistance of animals to such diverse toxic agents as beta-aminopropionitrile.

Deficient Proportions of Protein.—The influence of 10 per cent casein rations in lathyrus diets without the addition of other supplements on the formation of lathyritic bodies has also been studied. The food intake and consequently the amount of beta-aminopropionitrile were adequately controlled by paired feeding. All of the animals fed the 50 per cent sweet-pea diets or the protective diet I without supplements developed lathyritic bodies in the pulp but they appeared much later in the rats given the various protein and amino acid supplements and their incidence was reduced. Investigations utilizing amounts and proportions of proteins and amino acids that result in augmenting metabolism and growth of the host animal present two difficulties in the evaluation of effects on beta-aminopropionitrile. One is the factor of the significance of different caloric intakes. The other is related to the manner in which the nonsupplemented lathyrus diets are altered to prepare the control diet (protective diet I). It is obvious that this measure results in rations that differ not only in proportions of the particular amino

acid but also in the proportions of balanced adequate protein. At this point, one may ask whether an observed change in the formation of lathyritic bodies is due to the specific amino acid or to the resultant increase in adequate protein. In many instances the latter appears to be the correct explanation. Therefore, the conclusions of this investigation—that particular proteins and amino acids play a specific role in the genesis of the specific lathyritic bodies—seem substantial because of the many re-examinations that took place during the course of the study.

Influence of Proportions of Dietary Components.—Proteins represent a class of dietary components which are similar on the basis of nitrogen present in peptide bonds but which differ widely in component amino acids and in physical and biologic properties. It is therefore obvious that experiments on the effects of varying the components of the lathyrus diet can yield only particular data. Generalizations on the basis of collateral knowledge are necessary to give the results broader and more useful significance. If varying the proportion of casein or gelatin as the main source of protein in the presence of lathyrism is found to influence skeletal growth, body weight, and the formation of peculiar lathyritic bodies in the pulp, it is difficult to say with certainty that exactly similar results would not be obtained with other proteins or mixed sources. This fact should be understood in dental research, and it is of importance when the results obtained are interpreted with a particular member of a class. Designing an experiment, as in this study, which involves different proportions of nutritional components poses still another problem. Alterations in diet often lead to changes in body weight relative to that of the control animals. This may be consequent to a voluntary increase or decrease in caloric intake, or it may be determined, as in lathyrism, by an influence on the metabolism of the animal. Inasmuch as the genesis of lathyritic lesions in the pulp can be modified by a change in dietary components (caloric intake) and body weight, it becomes necessary to determine by logic and insight whether the observed effects on lathyritic body formation are due to the experimental modification or to the accompanying caloric and body-weight changes. This problem is difficult to surmount, even by the use of paired feeding, as in this investigation. Even under these conditions, there exist differences in absorption, composition, interconversions, and excretion which may effect notable differences in body weight (an excellent index of usable calories) and lathyritic lesions in the pulp.

Speculation on Nutrition in Relation to Lathyrism.—In the origin of the lathyritic pulp lesions, striking changes may be produced since the nutritional alteration modifies the amount of actual toxin reaching the site of action. Such a situation at various sites during lathyrism may not be uncommon. It is likely that, for many of the mesodermal alterations in lathyrism, dietary changes that do not seriously affect the health of the host animal modify only slightly the susceptibility of the target cells to the toxic compound. The initiation of lathyritic lesions in the pulp is probably influenced to a great extent

under these conditions. Therefore, in the origin of the lathyritic alterations (body), dietary supplementation plays an important role in modifying and sensitizing the target cells so that they become less vulnerable to the toxic compound, beta-aminopropionitrile. From the evidence gathered during the course of this investigation, it appears that for the most part nutritional alterations have their main effects during the developmental stage of the lathyritic lesion in the pulp. Whether these involve energy only or are intimately linked with essential cellular constituents is only a matter of conjecture at this time.

The mechanism of action of the dietary supplements may be attributed to differences in factors in the experimental groups, the potency of the toxin, and the way it reaches the site of action. Another determinant may be the varying effects of the particular dietary alteration on the respective tissues being acted upon by the lathyrus toxin.

The anatomy and the manifold functions of the dental pulp dispose it to a unique type of reaction. Its special blood supply and other properties provide for the intracellular composition to fluctuate widely with dietary changes. Moreover, this study provides facts that point out the pulp's great susceptibility to the action of toxic agents and necrotizing conditions. The toxic compound, deliberately administered, may affect the pulp directly. When more is known about the various sets of events that induce pulpal alterations and pulp disease and the way in which a particular set is modified by a change in the nutritional state of the host animal and in the pulp proper, many of the seemingly divergent effects may fit into a more consistent pattern. Although this investigation clearly demonstrates the agent and the alteration in the pulp during experimental lathyrism, our understanding of the way in which they act upon the cells and the cell environment to produce lathyritic bodies is meager. It is possible that a destruction of the mucopolysaccharide of the ground substance takes place in the pulp. The dietary supplementations and the consequent alteration in the nutritional state of the animal may influence the genesis of lathyritic bodies in the following ways: (1) by modifying the solubility, rate of metabolism, metabolic products, or amount of beta-aminopropionitrile toxin reaching the target tissue (the effective tissue dosage of actual beta-aminopropionitrile); (2) by modifying the susceptibility of the target cells to lathyritic-body-initiating action; and (3) by modifying the development of the initiated, biased cells.

These latter two influences involve not only cells but also their environment—cell surface, ground substance, stroma, and blood supply. In other words, nutritional effects may be mediated through changes in the dose of effective beta-aminopropionitrile, the initiatory stage, or the developmental stage. For the nutritional modification by supplementation of lathyrus diets, one or more of these possibilities exists. The influence may be determined systemically or locally, but the end result must be at the actual site of pulpal alteration.

SUMMARY AND CONCLUSION

This investigation of the dental pulp has as its purpose the study of the reaction of pulp tissue to an exogenous agent (sweet peas). In this investigation a series of changes have been tabulated to indicate the response of the pulp to the lathyrus toxin. The pulp reactions were due to a systemic influence, since all local factors and reactions to cavity preparation and to filling materials have been avoided. Protection of the dental pulp against the exogenous agent has also been investigated.

The following tissue changes are present during lathyrism and indicate a reaction of the pulp to the lathyrus toxin:

1. Eosinophilic zone alteration.
2. Cavity formations between the odontoblasts, in Weil's zone, and around cells in the cell-rich zone. The empty spaces occurred in the ground substance of the pulp.
3. A few odontoblastic nuclei in dentinal tubules.
4. Dilated and hyperemic capillaries, confined centrally in pulp tissue as well as in the odontoblastic layer, due to hyperproduction of capillaries.
5. Extravasation of erythrocytes, which is indicative of hemorrhage.
6. Reticular atrophy in the odontoblastic layer and in the central part of the pulp with degeneration. Reticular atrophy in this investigation is considered to be due to artifact exclusively and should not be construed as an aging process in the pulp. There is formation of large, confluent cavities in the odontoblastic layer. The predentine zone is irregular, but uninterrupted dentinal tubules ending between the odontoblasts can be distinguished. Nucleus-like bodies in dentinal tubules appear notably in the predentine zone. Cavity formations in the central pulp tissue, giving the appearance of reticular atrophy, also occur.
7. Shrinkage of odontoblasts.
8. Hyaline bodies or eosinophilic necrosis in the odontoblastic and adjacent zones.
9. Calcific degeneration and formation of denticles.
10. Dietary substances added to the lathyrus diet prevented the formation of cellular degeneration (reticular atrophy) throughout the pulp tissue and prevented hyaline necrosis in the odontoblastic and adjacent zone. In all groups fed protective diets (except those given P.D. VII), the dietary additions prevented new formation of capillaries invading the odontoblastic zone. Cellular invasions were similarly prevented in all groups fed protective diets with added substances.
11. Lesions resulting from degeneration of the mucopolysaccharides of the ground substance occur in pulpal connective tissue during lathyrism.

12. Lesions of lathyrism result from an interference with the rate of growth of pulpal connective tissue, and this is the most characteristic mechanism involved in the pulp.
13. The lathyrus factor, with its interference with the ground substance in combination with stress, must operate simultaneously to produce the resultant lesion. There is, therefore, some vital connection between the lathyrus factor and the mucopolysaccharides. Lathyrism shows capillary hemorrhages in specialized loose connective tissue of the pulp.
14. It is apparent that many of the metabolic derangements and aging processes start with degenerative and not inflammatory changes in mesenchymal tissues, and this is without exception the sequence in lathyrism. The most important tissues affected are connective tissue of ligaments and tendons and the specialized gelatinous, loose variety of the pulp. The skeleton and vascular tree undergo metabolic derangements with aging during lathyrism. These include dental pulp, joint cartilage degeneration, osteoporosis, and thoracic kyphoscoliosis.
15. Thus, in lathyrism an accentuation of the physiologic aging of mesenchymal tissue has occurred, and this has been demonstrated by means of the dental pulp.

It is concluded that modification of lathyritic alterations (eosinophilic bodies in the pulp) through a change in the proportion of dietary proteins and amino acids, within limits that permit relatively good growth and body weight, has so far been unequivocally demonstrated for the specific alterations in the dental pulp.

The influence of dietary proteins and amino acids is widely known to be demonstrated in the liver, but this investigation reflects their influence upon the dental pulp, an extrahepatic tissue. No doubt the observed effects upon the dental pulp are related to amounts of protein in the pulpal tissue that are marginal with respect to optimal pulpal health and function of this tissue.

Perhaps the use of similar conditions in other oral and dental tissues, with carefully controlled dietary intake and body weight, would reveal the influence of protein and amino acid supplementation on the intimate alterations leading to the development of changes in these tissues.

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BACTERIOLOGY

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THE INHIBITORY ACTION OF STIMULATED WHOLE SALIVA ON THE IN VITRO GROWTH OF CLOSTRIDIUM TETANI

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REVIEW of the pertinent literature reveals that infections caused by *Clostridium tetani* subsequent to oral trauma or oral surgical procedures occur rarely. Appleton[1] cites a fatality in which a typical strain of *Cl. tetani* was isolated from a periapical region and a fatal postextraction infection in which the exudate from the socket was found to contain morphologically typical tetanus bacilli. Other cases cited by Appleton were diagnosed either by clinical symptoms or by the response to the administration of tetanus antitoxin. Appleton comments: "... from the printed word it is often impossible to tell whether the word tetanus refers merely to a non-specific clinical condition characterized by jaw-cramp." The infrequency with which the oral cavity is a site of infection by this microorganism is further substantiated by the clinical and teaching experiences of two well-known oral surgeons,* ** neither of whom encountered a case of oral tetanus during spans of service of sixty and forty years, respectively. Recently Robinson and Laskin[2] reported a case of tetanus of oral origin which was confirmed by the isolation of *Cl. tetani* from both the extracted molar tooth and the exudate from the periapical region. They found only fifteen reported cases of oral infection by this microorganism in their review of the literature since 1910. Unfortunately, the majority of these cases were not confirmed by bacteriologic examination but were diagnosed essentially on the basis of clinical findings or recovery coincidental to tetanus antitoxin therapy.

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Three possibilities regarding the failure of *Cl. tetani* to colonize as members of the oral microbiota are (1) these microorganisms may seldom gain entrance into the oral cavity, (2) suitable environmental conditions do not obtain for spore germination or the propagation of vegetative cells, and (3) the indigenous microorganisms or inhibitory factors present in the oral cavity modify or inhibit colonization.

Entrance Into the Oral Cavity.—Tetanus spores are found most frequently in well-manured soils. Particles of soil adherent to vegetables may be a factor in their transportation. Tanner[3] has isolated *Cl. tetani* from vegetables. Wilson and Miles[4] state: "The tetanus bacillus must be ingested frequently with raw food but the evidence suggests that it is an organism of passage which does not find a natural habitat in the human intestine." Apparently *Cl. tetani* may frequently gain access to the mouth via food, water, and the hands. Hall[5] found obligate anaerobic sporulating bacilli in six of fifty-five specimens of saliva collected at various times from forty-three persons. One of these six clostridium species was the tetanus bacillus which he cultured from a saliva specimen obtained from the healthy mouth of his young daughter. Hall concluded that sporulating anaerobic bacilli are not commonly found in the oral cavity and that it is usually impossible to detect the same species in subsequent samples from the same mouth.

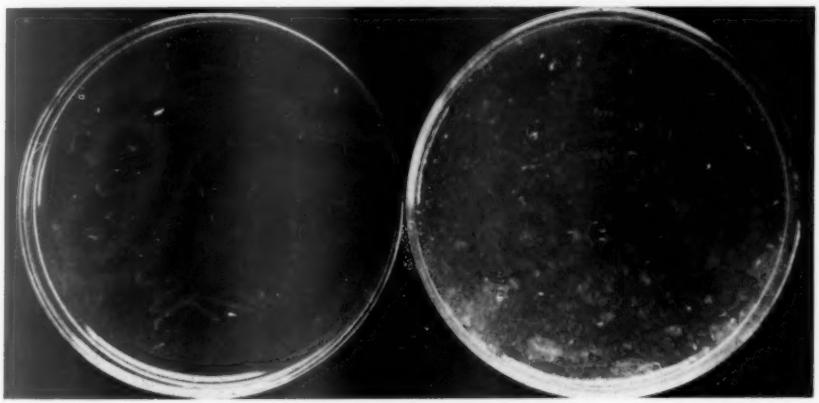
Suitable Environmental Conditions.—A large proportion of the total oral microbiota is anaerobic in character. Although free-flowing saliva has a positive redox potential which ranges between 240 and 400 millivolts,[6] it must be presumed that reducing potentials do obtain in the oral cavity to support the abundant anaerobic flora. Presumably, the interproximal space, the gingival sulcus, and the periodontal pocket provide such ecologic niches. Low oxidation-reduction potentials attain in the presence of metabolizing aerobes, suppurative and necrotic tissues, proteolytic products, and at alkaline pH's. From our knowledge of the in vitro nutritional requirements of *Cl. tetani,* it would appear that suitable environmental conditions exist in the oral cavity to support growth.

Inhibitory Factors.—Thompson,[7] Bibby,[8] and Berger,[9] among others, have demonstrated that saliva contains several factors of an antibacterial nature. Lysozyme is one which is effective in inhibiting the growth of a number of saprophytic microorganisms. Another factor is apparently associated with the oral microbiota. Recently, we reported on the activity of freshly stimulated saliva in inhibiting the in vitro growth of beta hemolytic streptococci.[10] The factor was found to be distinct from lysozyme; it was irreversibly destroyed by heat at 100° C. and was retained by Seitz and Berkefeld filters. The factor was associated with the actively growing oral microbiota and was active under anaerobic conditions and in the presence of blood, potato juice, or purified catalase. On the basis of the above criteria, it was considered to be distinct from hydrogen peroxide produced by certain of the oral microbiota during in vitro growth under aerobic conditions. It appears paradoxical that although (1) tetanus bacilli gain access to the mouth, (2) trauma (accidental or through

operative procedures) occurs in the mouth, and (3) conditions prevail in the oral cavity which permit obligate anaerobes to establish themselves as members of the permanent indigenous oral microbiota, infections of clostridial origin are so rare. This study was undertaken to determine whether freshly stimulated saliva contains some factor which may inhibit the in vitro growth of *Cl. tetani.*

METHODS AND RESULTS

Experiment 1. Determination of Presence in Saliva of an Antitetanus Bacillus Factor.—Brain-heart infusion agar (Difco) with sufficient agar added to give a 2 per cent concentration, was used as the basal medium. Stimulated saliva collected by chewing baseplate wax (Allcezon, Mizzy) previously tested and found not to be bactericidal, was added to 10 ml. of the basal medium cooled to 42° C. in 2.5 ml. aliquots to give a 25 per cent concentration by volume. Plates were poured, and the agar surface was streaked with a heavy inoculum of *Cl. tetani.* Suitable controls consisting of the medium without



A. *B.*

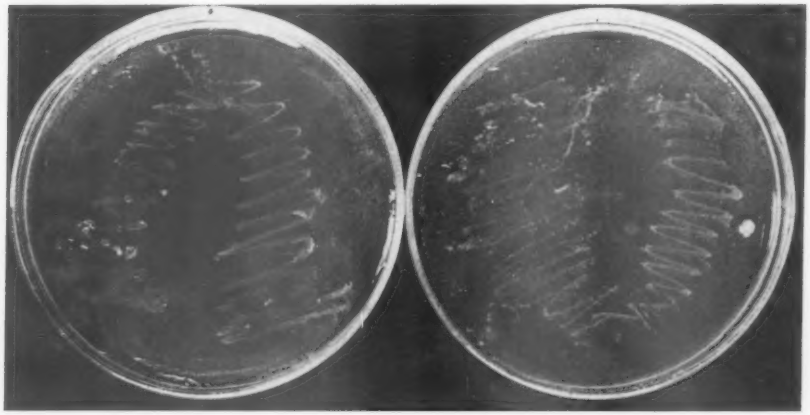
Fig. 1.—Brain-heart infusion agar with 25 per cent heated saliva (*A*) and 25 per cent fresh saliva (*B*). Incubated forty-eight hours under anaerobic conditions. Note on plate *A* the absence of colonies of the salivary microorganisms and the presence of surface growth of *Cl. tetani.* On plate *B* note the presence of colonies of oral microorganisms and the absence of surface growth of *Cl. tetani.*

saliva and the medium with 25 per cent saliva heated at 100° C. for 15 minutes to destroy the oral microbiota and enzymes were utilized. Plates were incubated under both aerobic and anaerobic conditions and observed at two- and 4-day intervals (Fig. 1).

Results: No observable growth of *Cl. tetani* occurred on the fresh unheated saliva plates, while good growth was found on the control plates. No growth occurred under aerobic conditions. Growth on the control plates was Gram stained and found to contain gram-positive bacilli with swollen terminal spores. Some of the growth was suspended in sterile saline and injected together with sterile calcium carbonate into the leg muscle of a guinea pig. A second pig was injected with an aliquot volume and also given 500 units of

tetanus antitoxin. The unprotected pig died within twelve hours, and the one given antitoxin was destroyed after five days when it began to show symptoms of spasmotic paralysis.

Experiment 2. Effect of Saliva on Cl. tetani Spores.—One milliliter of a heavy suspension of sporulating *Cl. tetani* was added to 20 ml. of freshly collected saliva. The mixture was kept at 37° C., and aliquots of 2 ml. were removed at intervals of twenty-four, forty-eight, and seventy-two hours, respectively. One aliquot was added directly to 10 ml. of melted brain-heart infusion agar, cooled to 42° C., while the other was heated at 85° C. for twenty minutes to destroy vegetative forms of the oral microbiota and tetanus bacillus. Plates were poured and incubated under anaerobic conditions at 37° C. for four days.



A. *B.*

Fig. 2.—Brain-heart infusion agar with 25 per cent Seitz-filtered saliva (*A*) and purified lysozyme 1:1,000 (*B*). Note on plate *A* growth of *Cl. tetani* and absence of colonies of oral microflora. On plate *B* note that lysozyme does not inhibit the growth of *Cl. tetani*.

Results: Growth of the tetanus bacillus was inhibited by the unheated saliva portion, whereas growth was not restrained by the heated portion. Apparently, tetanus spores are not destroyed by the oral microbiota, but their germination is inhibited.

Experiment 3. Effect of Bacterial Free Saliva Filtrate on Cl. tetani.—Stimulated saliva was filtered through the Seitz bacterial filter and tested as described above. Suitable controls of the basal medium alone and with fresh saliva and heated saliva were run.

Results: Cl. tetani grew well on the surface of the medium containing 25 per cent of Seitz-filtered saliva. No colonies of the oral microbiota were observed. The medium without saliva or with heated saliva likewise supported good growth. Fresh unheated saliva inhibited the proliferation of the tetanus bacillus (Fig. 2, *A*).

Experiment 4. Effect of Lysozyme on Cl. tetani.—Purified lysozyme 1:1,000 was added to the basal medium. Plates were streaked with *Micrococcus lysodeikticus* and with *Cl. tetani.* Incubation was both aerobic and anaerobic. Control plates containing heated and unheated saliva were also made.

Results: The presence of lysozyme had no effect on the growth of *Cl. tetani,* while it completely inhibited the growth of *M. lysodeikticus.* The control plate containing the fresh saliva inhibited growth of the tetanus bacillus and also of *M. lysodeikticus.* The heated saliva had no effect on either microorganism (Fig. 2, *B*).

Experiment 5. Effect of the Addition of Oral Bacteria to Heated Saliva Basal Medium on the Growth of Cl. tetani.—The mixed surface growth obtained from a blood plate previously streaked with a loopful of saliva was added to the heated saliva basal medium. Control plates containing the basal medium alone, basal medium with heated saliva, and basal medium with unheated saliva were also prepared. The plates were incubated anaerobically.

Fig. 3.—Inhibition of growth of *Cl. tetani* by an anaerobic micrococcus.

Results: Cl. tetani did not grow on the heated saliva medium containing the inoculum of the salivary microbiota. Likewise, no growth occurred on the control plate containing fresh saliva. Good growth appeared on the basal medium plus the heated saliva (Fig. 3).

DISCUSSION

Freshly stimulated whole saliva contains a factor which under in vitro experimental conditions inhibits the growth of *Cl. tetani.* It appears distinct from lysozyme, since crystalline purified lysozyme 1:1,000 had no observable effect on the tetanus bacillus while inhibiting completely *Micrococcus lysodeikticus.* Heating the saliva for fifteen minutes at 100° C. and filtration through the

Seitz filter eliminate the oral microbiota and the inhibiting factor. The addition to heated saliva basal medium plates of the mixed surface growth obtained from an aerobic blood plate previously streaked with a loopful of saliva inhibited the growth of the tetanus bacillus. It appears that the antitetanus bacillus factor is associated with the viable oral microorganisms. Spores of the tetanus bacillus are not destroyed on exposure for three days to saliva and its indigenous microflora. Their germination is not inhibited when the oral microbiota are either destroyed by heat or removed by filtration. In the absence of unfavorable environmental conditions, two factors may determine whether a given microorganism can establish itself in a particular habitat. Limitation of growth may result from "population pressure" or absence of "Lebensraum" or from the production of inhibitory substances by the viable oral microorganisms.

SUMMARY

Freshly stimulated saliva exhibits an inhibitory action toward the tetanus bacillus. The factor is distinct from lysozyme and is not filterable through the Seitz filter. It appears to be associated with the oral microbiota. Exposure of tetanus spores to the oral microbiota does not destroy them but does inhibit their germination.

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ESTERASE ACTIVITY ASSOCIATED WITH FORMATION OF DEPOSITS ON TEETH

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INTRODUCTION

ALTHOUGH enzyme systems associated with the normal calcification process have been studied,[1-3] a search of the literature failed to reveal any publications relating to known enzyme systems, other than phosphatases,[4] associated with pathologic calcification. The formation of calcified deposits on teeth may be considered a pathologic or ectopic type of calcification. In the present work, procedures were employed for the histochemical demonstration of esterase in such early deposits. These deposits, although not always calcified, are nevertheless frequently referred to by the generic term "calculus." The present work represents the first report in the literature of enzyme histochemistry as a tool in the study of calculus formation. In addition, histochemical demonstration of esterase activity in bacteria is described.

MATERIALS AND METHODS

Mylar strips, 6.5 μ thick (Mylar 25C), were fastened to the lingual surfaces of the lower incisor teeth of patients who were admitted with a diagnosis of periodontitis. A total of sixty-five strips were obtained from twenty-five patients, all of whom were between the ages of 25 and 38 years. Their teeth were thoroughly cleaned and polished before the strips were applied. The Mylar strips were allowed to remain secured for periods varying from three to thirty days. However, a seven-day period was generally employed.

In preliminary studies, strips of celluloid and nylon were tried, and some preparations were also made by scraping deposits directly from the tooth surfaces. They were discontinued in favor of the 6.5 μ mylar, however, when it was found that the results obtained were not quite as satisfactory.

From the National Institute of Dental Research, National Institutes of Health, United States Department of Health, Education, and Welfare.

Upon removal, the strips were incubated in substrate solutions to reveal the presence of esterase activity. Acetates of AS-naphthols were chosen as substrates because of the potential chromogenicity and insolubility of the enzymatically released naphthol. These factors facilitate good localizations at high optical magnification. A mixture of acetates of naphthol AS-D (3-hydroxy-2-naphtho-o-toluidide) and naphthol AS-LT (3-hydroxy-2-methyl-2-naphth-p-anisidide) were used. This mixture tends to reduce crystallization, which may occur when an azo dye from a single naphthol is produced. Data on naphthol AS-LT acetate are as follows:

$C_{21}H_{19}O_4N$, m.w. 349-37 analysis calcd. C72.19, H5.48, N4.01
found* C72.24, H5.44, N4.06

For use, approximately 5.0 mg. AS-D acetate and 5.0 mg. AS-LT acetate was dissolved in 0.5 ml. DMF (N,N-dimethyl-fornamide) followed by 25.0 ml. of distilled water and 25.0 ml., 0.2 M Tris buffer, pH 7.1 (24.2 GM Tris (tris hydroxymethylaminomethane) plus 189 c.c. 1 N hydrochloride with distilled water to make 1,000.0 ml.). Then 30 mg. of diazotized o-aminoazotoluene (Garnet GBC salt† was added, and the mixture was shaken and filtered through a rapid filtering paper into a Coplin jar. The Mylar strips were then incubated for one hour at room temperature.

A series of potential esterase inhibitors were interposed during the reaction period. These included physostigmine salicylate, 10-4 M; sodium fluoride, 0.003 M; benzethonium (Phemerol) chloride, 1:1,000; benzalkonium (Zephiran) chloride, 1:1,000‡; diisopropyl fluorophosphate (DFP), 10^{-4}M.‡ Representative sections of strips were also preincubated in hot water (90° C.).

Following staining, an alcian blue counterstain (for nuclei) was used in some cases. The stained strips were mounted in a glycerol-gelatin or a polyvinyl pyrrolidone medium.

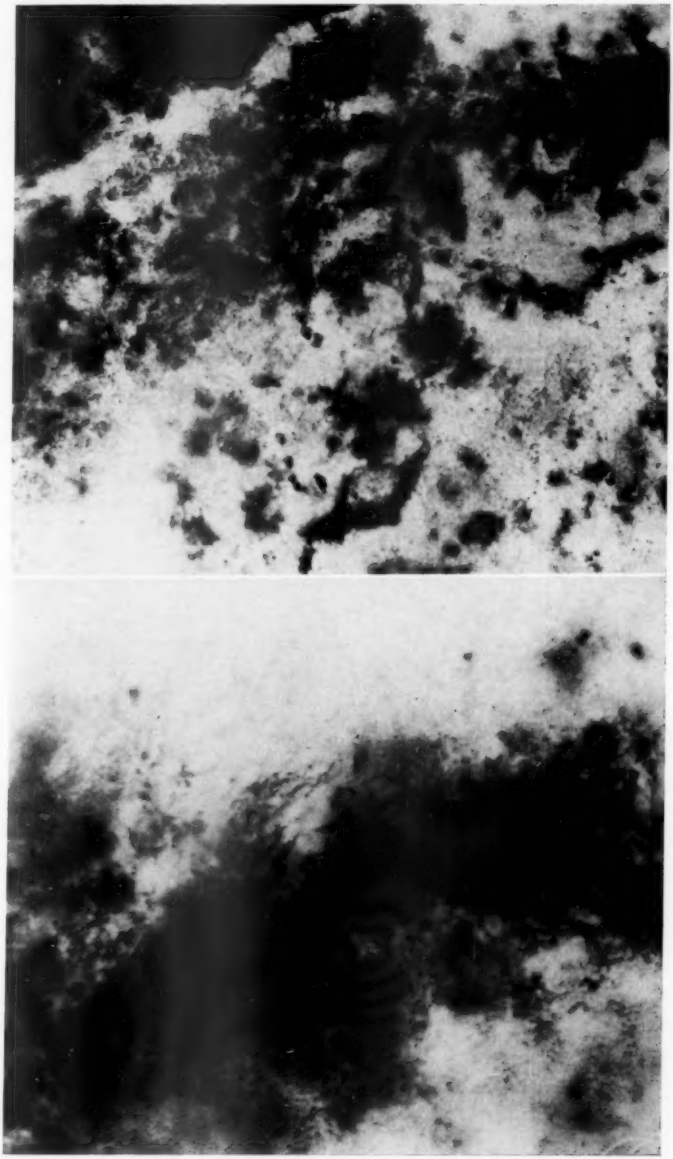
OBSERVATION

The bulk of the deposits on the strips consisted of clumps of coccoid and filamentous forms of bacteria. Cocci, which were the first to appear, were present on all strips and were the most abundant form. Also present in varying numbers were polymorphonuclear leukocytes, macrophages, and desquamated epithelial cells. These observations are essentially in agreement with the findings of Mandel and colleagues.[5]

Esterase activity was discernible as an intense red stain. Cocci, which always stained red, showed the highest activity (Fig. 1, *A*). By contrast, filamentous forms showed variable staining (Fig. 1, *B*). Esterase activity of polymorphonuclear leukocytes (Fig. 2, *A*), macrophages, and epithelial cells (Fig. 2, *B*) was indicated by the presence of stained intracellular cytoplasmic

*Microanalyses by Dr. W. Alford and group.
†General Dyestuff Corp., New York, New York.
‡Sections pretreated with potential inhibitor for one hour prior to incubation. All other inhibitors were incorporated in the substrate mixture.

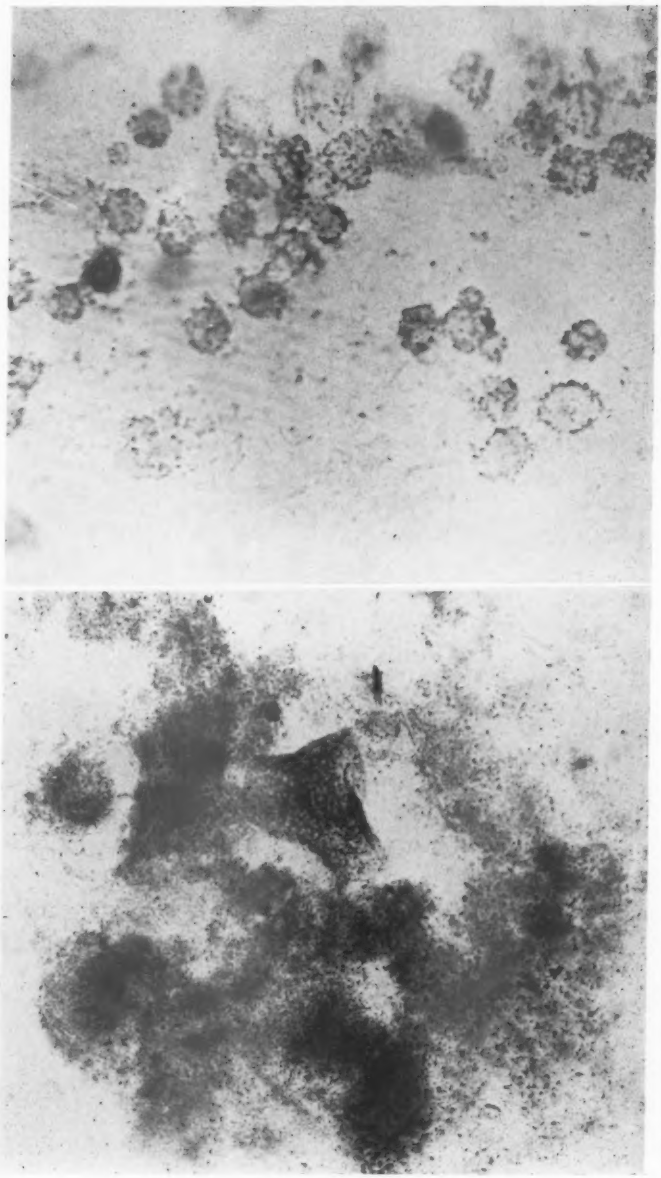
A.



B.

Fig. 1.—The dark areas (actually stained a bright red) are colonies of (*A*) cocci and (*B*) filamentous organisms exhibiting esterase activity. (Magnification, ×1,200.)

A.



B.

Fig. 2.—Esterase activity of (*A*) polymorphonuclear leukocytes and (*B*) epithelial cells showing granular distribution of activity. (Magnification, ×300.)

granules. The esterase activity appeared to be correlated with cell vitality in that it disappeared as the cells degenerated. To rule out the possibility that some of the (stained intracellular) cytoplasmic granules of the aforementioned cells were not merely due to adherent or ingested bacterial forms, these were compared with similar cells from oral and blood smears. In this manner, confirmation that the cytoplasmic granules in the cells exhibited genuine esterase activity was obtained.

Hot water, benzalkonium chloride, and eserine produced distinct inhibition, while the effect of the remaining inhibitors was not marked.

DISCUSSION

Bone and dentine matrices, during early stages of normal calcification, have been found to be capable of hydrolyzing the same substrates as used in this study. However, the effect of inhibitors upon this reaction differed from that associated with deposit formation on teeth.[2]

The view has been held from time to time that fatty acid esters represent a determining factor in pathologic calcifications by means of a saponification mechanism. Haas,[6] for example, reports that the granules between fibrils in a calcifying zone may possess a lipoidal component. In any event, hydrolysis of fatty acid esters by enzyme (esterase) activity may release fatty acids which are presumably capable of forming calcium and magnesium soaps. These soaps may then undergo transformation into the less soluble phosphate and carbonate.[6] Soap formation thus offers an explanation for the appearance and consistency of early deposit formations.

It is interesting to note that the pathologic calcifications frequently occur in areas where there is a breakdown of fat. Tubercles, atheromatous lesions, zones of fat necrosis, and lipomas may exhibit calcifications. Calculus is also known to contain fat and fatty acids.[5, 8] Thus there is suggested the possibility that calculus formation may be initiated by enzyme action followed by a saponification process.

Furthermore, the present study suggests the further use of azo dye techniques for the study of enzyme activity in bacteria.

SUMMARY

1. Esterase activity was found in bacteria, polymorphonuclear leukocytes, macrophages, and epithelial cells associated with deposit formation on teeth.

2. It is suggested that enzyme activity in tooth deposits it correlated with a saponification process, ultimately leading to calcifications.

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Erratum

In the article by Alling and Pulaski entitled "Current Trends in Antibiotics in Oral Surgery," which begins on page 743 of the June issue, the last sentence of the paragraph on nystatin on page 750 should read as follows:

> However, for the usual relatively short course of broad-spectrum antibiotic therapy as practiced in dentistry, the routine concurrent administration of nystatin and the broad-spectrum antibiotic is contraindicated.

ANNOUNCEMENTS

New York Institute of Clinical Oral Pathology, Inc.

A course in clinical oral pathology will be given two Wednesday evenings monthly from October through May. Sessions will last from 7:30 to 10 P.M. The class is limited to thirty students.

Lectures will be given on embryology, hematology, histology and pathology, and their clinical interpretation. The staff of the Institute and guest lecturers will present case reports stressing history, clinical findings, x-ray studies, diagnosis, treatment, and prognosis. The course is approved by the Board of Education of the University of the State of New York.

Inquiries should be addressed to the Executive Secretary, 101 East 79th St., New York 21, New York.

Mid-Continent Dental Congress

The Mid-Continent Dental Congress will be held Nov. 1 to 4, 1959, at the Chase-Park Plaza Hotels in St. Louis, Missouri. The Congress will feature one of the most unusual dental programs ever presented. The entire program will be given by the Indianapolis Dental Research Group under the direction of Dr. John Geller. The following are some highlights of the Congress:

Sunday, November 1.

Four-hour course on "An Approach to Patient Management," presented through skits, acting, and audience participation.

Human Relations in the Dental Office. Stanleigh B. McDonald, B.S., President, Scientific Education Associates, Inc.

An Approach to Patient Management (continuation of skits).

November 2, 3, and 4.

Fourteen lectures on various phases of dentistry.

Continuous consultation—table clinics by all essayists each day of meeting.

General table clinics—scientific and health exhibits—hobby exhibits—wonderful social events.

Special Event: A. D. A. Centennial Luncheon with Dr. Paul H. Jeserich, president of the American Dental Association, speaker.

Further information may be obtained from James E. Brophy, Executive Secretary, St. Louis Dental Society, 8013 Maryland Ave., St. Louis 5, Missouri.

Society of Oral Physiology and Occlusion

The sixth annual meeting of the Society will take place on Saturday, Dec. 5, 1959, in the Empire Room at the Hotel New Yorker, 34th St. and 8th Ave., New York City. The

seminar will be scheduled from 9 A.M. to 5 P.M., and the subject will be "Pain and the Temporomandibular Joint." Among the speakers will be Janet Travell, Joseph J. Martini, and Clyde B. Kyne.

Those interested in joining this organization should get in touch with Dr. S. M. Kelner, Secretary, 57 West 57th St., New York 19, New York.

Dental Guidance Council for Cerebral Palsy

The annual scientific meeting will be held in the Washington Room of the Hotel Statler, 32nd St. and Seventh Ave., New York, New York, at 8 P.M., Thursday, Nov. 12, 1959. The program follows.

8 P.M. Film Presentation: "Dental Care of the Cerebral Palsy Child."

8:30 P.M. Symposium (Bernard S. Friedman, Chairman). The panelists and their subjects are as follows:

Annette Zaner: Communication Impairments in Cerebral Palsy.

Adam Munz: Body Image Disturbances and Their Implications With Reference to the Mouth.

Solomon N. Rosenstein and Marvin King: Dental Care for the Older Cerebral Palsy Patient.

First District Dental Society

The Section on Oral Surgery of the First District Dental Society of the State of New York announces that a meeting will be held at 8 P.M., Wednesday, Oct. 21, 1959, on the tenth floor of the Hotel Statler in New York City. Dr. Leonard Monheim will present a paper on "Local Anesthesia in Dental Practice."

Georgetown University

The Georgetown University School of Dentistry in Washington, D. C., announces the following postgraduate courses:

1. Function, Prime Object of Dentistry. Arne G. Lauritzen, L.D.S., D.D.S. Oct. 7-10, 1959.
2. Refresher Course for Orthodontists in Clinical Occlusion. Arne G. Lauritzen, L.D.S., D.D.S. Oct. 13-15, 1959.
3. Advanced Working Course #1 in "The Technique of Functional Occlusal Analysis." Arne G. Lauritzen, L.D.S., D.D.S. Oct. 17-20, 1959.

Massachusetts Memorial Hospitals

The Department of Stomatology, Division of Graduate Studies, School of Medicine, Boston University, announces the following postgraduate courses:

Tooth Preparation and Elastic Impression Materials in Crown and Bridge. Arthur Kahn. Oct. 15-17, 1959.

Periodontal Therapy. Henry M. Goldman, Bernard S. Chaikin, Gerald M. Kramer, William Pendergast, and associates. Oct. 19-24, 1959.

Technics in the General Practice. Henry M. Goldman, David J. Baraban, Leo Talkov, Herbert Schilder, Gerald Kramer, Chester Landy, and Harold Berk. Oct. 26-31, 1959.

Occlusal Adjustment. Bernard S. Chaikin, Henry M. Goldman, Gerald M. Kramer, William Pendergast, and associates. Nov. 2-7, 1959.

Full Denture Prosthesis. Chester Landy. Nov. 9-13, 1959.

Fixed Bridge Prosthesis. Leo Talkov and David J. Baraban. Nov. 16-20, 1959.

Endodontics. Herbert Schilder. Nov. 30-Dec. 4, 1959.

Oral Pathology for Oral Surgeons. Jack Bloom, Henry M. Goldman, and Kurt H. Thoma. Jan. 11-16, 1960.

Removable Partial Denture Prosthesis. David J. Baraban. Jan. 21-23, 1960.

For further information, write to Director of Post-Graduate Studies, Department of Stomatology, Massachusetts Memorial Hospitals, 750 Harrison Ave., Boston 18, Massachusetts.

University of Minnesota

The Division of Oral Pathology of the School of Dentistry, University of Minnesota, is one of five schools to be granted a Fellowship in Clinical Oral Pathology by the American Cancer Society for the period July 1, 1960 to June 30, 1961. This Fellowship will pay the recipient $3,600.00 per annum, tax-free, and is renewable upon approval of the American Cancer Society.

A program of education has been synthesized to give the trainee advanced experience in both clinical and basic material in dermatology, dermatopathology, biostatistics, tumor pathology, advanced oral pathology, pediatrics, and metabolic and endocrine disorders. A wealth of clinical material is available within the University of Minnesota Medical Center.

Applicants must apply before Feb. 15, 1960, forwarding a curriculum vitae and academic record. Inquiries should be addressed to Dr. Robert J. Gorlin, Chairman, Oral Pathology, School of Dentistry, University of Minnesota, Minneapolis 14, Minnesota.

Saint Louis University

Alumni of Saint Louis University School of Dentistry will meet for dinner on Thursday, Sept. 17, 1959, during the American Dental Association meeting in New York. The dinner meeting will be held at the Commodore Hotel and will feature an address by Dr. Stephen P. Forrest, dean of the University's dental school. Dr. Theodore L. Jerrold of Brooklyn has been named chairman of the dinner program.

REVIEWS OF THE LITERATURE

ABTSRACTS OF CURRENT LITERATURE

The Significance of Liver Dysfunction in Mouth Cancer. N. Trieger, G. W. Taylor, and D. Weisberger: Surg. Gynec. & Obst. **108**: 230, February, 1959.

Mouth cancers comprise about 5 per cent of all cancers. Etiologically, squamous-cell carcinoma of the mouth has been associated with syphilis, chronic irritation, carcinogenic tars, and use of tobacco and alcohol. The apparent predilection to oral carcinoma of a small segment of the population suggests probable predisposing factors.

The present study was undertaken to identify further the incidence of liver dysfunction in patients with cancer of the floor of the mouth, palate, and tonsillar fossa.

Of the total of 152 patients, 68 had recorded information relative to the five "etiologic categories": tobacco and alcohol consumption, syphilis, oral irritants, and hepatic disease.

Data are presented showing a sex incidence of 7.5 males to 1 female with oral cancer. Survival studies indicate a significant difference if the patients are presented in two distinct groups, that is, those with hepatic cirrhosis and those without demonstrable hepatic cirrhosis. Cirrhotic patients with mouth cancer have a 19 per cent five-year survival rate, while 40.3 per cent of those patients without cirrhosis survive at least five years.

This report is subject to the numerous problems inherent in a retrospective study. Hospital records are frequently inadequate when they are re-evaluated in a search for specific data. Notwithstanding the limitations of this method, a large number of cases is available. This serves as a reliable guide to a study on the etiology of cancer of the mouth.

T. J. C.

Cementoma of Maxilla. R. L. Johnson and R. Cabanas: Bull. Millard Fillmore Hosp. **6**: 135, 1958-59.

Cementum is a highly specialized dental tissue of mesenchymal origin which arises from the connective tissue of the dental sac. It covers the root surfaces of teeth and invaginates for a short distance at the apical end of the root canal. The stimulation for the migration of the parent cementoblasts to their peripheral root position is unknown, but the sheath of Hertwig has been suggested as initiating this response.

In the case reported, at the time of surgery, following removal of the intact cementoma, the crown of the impacted third molar could be directly visualized. The follicular membrane was not intact. In the roentgenograms, that surface of the cementoma adjacent to the impacted third molar was the least calcified area of the lesion, suggesting immaturity. Another point of interest is the position of the impacted tooth in relation to the tumefaction. This latter point would tend to fix the site of origin of the tumor in a position distal to the second molar and inferior to the developing third molar within the tuberosity. Antral invasion can be explained on the basis of least resistance.

The authors agree that the etiology of cementoma is unknown.

T. J. C.